PATENT
Docket No. 265.00390101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Boldogh et al.	Group Art Unit:	1653
Serial No.:	10/691,330	Examiner:	Chih Min Kam
Confirmation No.:	1384		
Filed:	October 22, 2003		

For: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF AS INHIBITORS OF APOPTOSIS AND OTHER CELLULAR DAMAGE

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Nancy A. Johnson, declare and say as follows:

1. I am a patent attorney employed by Mueting, Raasch & Gebhardt, P.A., Minneapolis, Minnesota.

2. I have reviewed U.S. Patent No. 6,903,068 (U.S. Patent Application No. 09/641,801), issued on June 7, 2005.

3. For U.S. Patent No. 6,903,068 (U.S. Patent Application No. 09/641,801), I have reviewed the Specification and the Sequence Listing (filed on August 17, 2000), a Preliminary Amendment with Appendix (filed on June 11, 2001), an Amendment and Response with Appendix (filed on December 4, 2002), an Amendment and Response under 37 C.F.R. §1.116 (filed on June 5, 2003), an Amendment and Response (filed on November 3, 2003), an Amendment and Response (filed on February 9, 2004), an Amendment and Response (filed July 28, 2004), and an Examiner's Amendment received with the Notice of Allowance mailed

November 2, 2004. Copies of all of these documents are included with **Exhibit A.**

4. I have reviewed U.S. Patent Application 10/691,157 (published application 2004026681), filed October 22, 2003.

5. Upon information and belief, I hereby state that for U.S. Patent No. 6,903,068, the complete specification, as issued, is not the same as the specification, as filed, including amendments. Column 1, line 5, through column 19, line 37, of U.S. Patent No. 6,903,068, as issued, are incorrect.

6. Upon information and belief, I hereby state that U.S. Patent No. 6,903,068, as filed, included no drawings, while U.S. Patent No. 6,903,068, as issued, includes nine drawings.

7. Upon information and belief, I hereby state that U.S. Patent Application 10/691,157 (published application 2004 026681), filed October 22, 2003, has incorrectly printed as U.S. Patent No. 6,903,068.

8. Upon information and belief, I hereby state that a request for the issuance of a corrected patent pursuant to 37 C.F.R. § 1.322(b) was filed with the U.S. Patent and Trademark Office for U.S. Patent No. 6,903,068 on March 2, 2006. A copy this request is included in accompanying **Exhibit A.**

9. I submit that a reasonable person would conclude from the results and statements in paragraphs 2-8 above, that the information printed in issued U.S. Patent No. 6,903,068 contains substantial errors and does not correctly represent the information taught by this patent.

10. I submit that a reasonable person would conclude from the results and statements in paragraphs 2-9 above, because of the substantial errors in issued U.S. Patent No. 6,903,068, one must look only to the application itself, U.S. Patent Application No. 09/641,801, for a correct representation of what is taught by U.S. Patent No. 6,903,068.

11. I further declare that statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

March 17, 2006
Date

Nancy A. Johnson
Nancy A. Johnson

Exhibit A

Exhibit A

Receipt is hereby acknowledged for the following in the U.S. Patent and Trademark Office:
Applicant(s):Stanton et al.
Patent No. 6,903,068 Issued: June 7, 2005
Title: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

DKT 2

Enclosed: Request for Issuance of Corrected Patent (2 pgs.); Copies of previously filed documents (copies of: Specification and the Sequence Listing filed August 17, 2000; Preliminary Amendment with Appendix, filed June 11, 2001; Amendment and Response including Appendix, filed December 4, 2002, Amendment and Response under 37 C.F.R. §1.116, filed on June 5, 2003, including Auto-Reply Facsimile transmission sheet; Amendment and Response, filed on November 3, 2003; Amendment and Response, filed on February 9, 2004; Amendment and Response, filed on July 28, 2004; and Examiner's Amendment received with the Notice of Allowance, mailed November 2, 2004) and date-stamped returned postcard receipt of these items; and transmittal document (in triplicate).

OIPE IAP2 MAR 02 2006 PATENT & TRADEMARK OFFICE

Mailed: March 2, 2006
Docket: 265.00230101

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EMS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Stanton et al.	) Docket No.	265.00230101
Patent No.:	6,903,068 B1	)	
Issued:	7 June 2005	)	
For:	USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

We are transmitting the following documents along with this Transmittal Sheet (which is submitted in triplicate):

X **Small entity status is entitled to be asserted in the above-identified application.**

X An itemized return postcard.

X Request for Issuance of Corrected Patent (2 pgs.);

X Copies of previously filed documents (copies of: Specification and the Sequence Listing filed August 17, 2000; Preliminary Amendment with Appendix, filed June 11, 2001; Amendment and Response including Appendix, filed December 4, 2002; Amendment and Response under 37 C.F.R. §1.116, filed on June 5, 2003, including Auto-Reply Facsimile transmission sheet; Amendment and Response, filed on November 3, 2003; Amendment and Response, filed on February 9, 2004; Amendment and Response, filed on July 28, 2004; and Examiner's Amendment received with the Notice of Allowance, mailed November 2, 2004) and date-stamped returned postcards of each of these items.

Please consider this a PETITION FOR EXTENSION OF TIME for a sufficient number of months to enter these papers and please charge any additional fees or credit overpayment to Deposit Account No. 13-4895. Triplicate copies of this sheet are enclosed.

MUETING, RAASCH & GEBHARDT, P.A.
Customer Number: 26813

By: Nancy A. Johnson
Name: Nancy A. Johnson
Reg. No.: 47,266
Direct Dial: 612-305-4723
Facsimile: 612-305-1228

CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: EV 201894773 US Date of Deposit: March 2, 2006
I hereby certify that the Transmittal Letter and the paper(s) and/or fee(s), as described hereinabove, are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Sara E. Wigant
Name: Sara E. Wigant

(SMALL ENTITY TRANSMITTAL UNDER RULE 1.10)

PATENT
Docket No. 265.00230101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Stanton et al.	)
		)
Patent No.:	6,903,068 B1	)
		)
Issued:	7 June 2005	)
		)
For:	USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES	

REQUEST FOR ISSUANCE OF CORRECTED PATENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The issuance of a corrected patent, pursuant to 37 C.F.R. § 1.322(b), is requested to correct significant printing errors appearing in the above-identified United States Patent, which was issued on June 7, 2005.

Applicant's representatives have identified the following errors:

The complete specification, as issued, is not the same as the specification, as filed, including amendments, for the above-identified United States Patent. Column 1, line 5, through column 19, line 37, of the above-identified United States Patent, as issued, are incorrect.

The above-identified United States Patent, as filed, included no drawings, while the above-identified United States Patent, as issued, includes nine drawings.

The "Related Applications Data" on the face page of the above-identified United States Patent, as issued, is incorrect. The above-identified United States Patent claims priority to U.S. Provisional Application 60/149,311, filed August 17, 1999.

It appears that U.S. Patent Application 10/691,157, filed October 22, 2003, has mistakenly printed instead of the above-identified United States Patent (U.S. Patent Application 09/641,801, filed on August 17, 2000).

All of these mistakes are mistakes on the part of the U.S. Patent and Trademark Office. Enclosed, as evidence of the U.S. Patent and Trademark Office errors indicated above, are copies of the Specification and the Sequence Listing, as filed on August 17, 2000, a Preliminary Amendment with Appendix, filed on June 11, 2001, an Amendment and Response with Appendix, filed on December 4, 2002, an Amendment and Response under 37 C.F.R. §1.116, filed on June 5, 2003, including Auto-Reply Facsimile Transmission sheet, an Amendment and Response, filed on November 3, 2003, an Amendment and Response, filed on February 9, 2004, an Amendment and Response, filed July 28, 2004, and an Examiner's Amendment received with the Notice of Allowance mailed November 2, 2004. Also enclosed are copies of the date-stamped returned post cards for each of the previously listed items.

Applicant's representatives submit that the nature of the mistakes on the part of the U.S. Patent and Trademark Office are such that a certificate of correction is inappropriate. Pursuant to 37 C.F.R. § 1.322(b), Applicant's representatives request that the Director issue a corrected patent, without expense to the patentee.

Please mail the corrected patent to the undersigned attorney along with four advance order copies which have already been charged to our account with the payment of the Issue Fee on February 2, 2005.

CERTIFICATE UNDER 37 C.F.R. 1.10:

The undersigned hereby certifies that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated below and is addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Sara E. Wegant

Name: Sara E. Wegant
"Express Mail" mailing label number:
EV 201894773 US
Date of Deposit: March 2, 2006

March 2, 2006
Date

Respectfully submitted
By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612)305-1220
Facsimile: (612)305-1228
Customer Number 26813

By: Nancy A. Johnson
Nancy A. Johnson
Reg. No. 47,266
Direct Dial (612)305-4723

Exhibit A

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Receipt is hereby acknowledged for the following in the U.S. Patent and Trademark Office:

Applicant(s): G. John STANTON of [redacted] City, Texas
Thomas K. HUGHES, Jr. of Galveston, Texas
Istvan BOLDOGH of Galveston, Texas
Jerzy A. GEORGIADES of Houston, Texas

jc:862 U.S. PTO
09/641801
08/17/00

Title: **USE OF OLIGOSTRININ, CONSTITUENT PEPTIDES THEREOF AND ANALOGS THEREOF FOR INDUCING CYTOKINES**

Enclosed: Utility Patent Application: Specification (33 pgs); Claims (36 claims on 8 pgs); 1 pg Abstract; and Sequence Listing (9 pgs.); Communication regarding sequence listing (1 page); Computer Readable Form of Sequence Listing (1 diskette)

Mailed: 17 August 2000

Docket No.: 265.0023 0101

AMM:lmg

EL518336573US

Applicant: Stanton et al.
Serial No: unknown
Filed: 17 August 2000
Title: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

COMPUTER READABLE FORM:
Medium Type: Diskette
Computer: IBM PC compatible
Operating System: PC-DOS/MS-DOS
Software: PatentIn Release #2.0

Date Recorded: 17 August 2000 265.0023 0101

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Applicant: Stanton et al.
Serial No: unknown
Filed: 17 August 2000
Title: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

COMPUTER READABLE FORM:
Medium Type: Diskette
Computer: IBM PC compatible
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Software: PatentIn Release #2.0

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USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

Cross-Reference to Related Applications

The present application claims priority from U.S. Patent Application Serial No. 60/149,311, filed on August 17, 1999, which is incorporated herein by reference.

Background of the Invention

Colostrum is a component of the milk of mammals during the first few days after birth. Colostrum is a thick yellowish fluid and is the first lacteal secretion post parturition and contains a high concentration of immunogloblins (IgG, IgM, and IgA) and a variety of non-specific proteins. Colostrum also contains various cells such as granular and stromal cells, neutrophils, monocyte/macrophages, and lymphocytes. Colostrum also includes growth factors, hormones, and cytokines. Unlike mature breast milk, colostrum contains low sugar, low iron, but is rich is lipids, proteins, mineral salts, vitamins, and immunoglobins.

Colostrum also includes or contains a proline-rich polypeptide aggregate, which is referred to as colostrinin. One peptide fragment of colostrinin is Val-Glu-Ser-Tyr-Val-Pro-Leu-Phe-Pro (SEQ ID NO:31), which is disclosed in International Publication No. WO-A-98/14473. Colostrinin and this fragment have been identified as useful in the treatment of disorders of the central nervous system, neurological disorders, mental disorders, dementia, neurodegenerative diseases, Alzheimer's disease, motor neurone disease, psychosis, neurosis, chronic disorders of the immune system, diseases with a bacterial and viral aetiology, and acquired immunological deficiencies as set forth in International Publication No. WO-A-98/14473.

Although certain uses for colostrinin have been identified, it would

represent an advancement in the art to discover and disclose other uses for colostrinin, or a component thereof, that are not readily ascertainable from the information currently known about colostrinin or its constituents.

SUMMARY OF THE INVENTION

The present invention relates to the use of colostrinin, at least one constituent (i.e., component) peptide thereof, at least one active analog thereof (e.g., peptide having an N-terminal sequence equivalent to an N-terminal sequence of at least one of the colostrinin constituent peptides), and combinations thereof, as a cytokine-inducing agent. These agents can be used as immunological regulators to modulate (e.g., enhance, inhibit, modify, augment, or otherwise alter, and preferably promote) specific or nonspecific immune responses in patients, particularly animals including mammals such as humans. They can also be used as blood cell regulators to modulate (e.g., enhance, inhibit, modify, augment, or otherwise alter, preferably, and promote) cellular proliferation or differentiation (preferably, promoting proliferation and differentiation) of blood cells, such as leukocytes.

In one embodiment, the present invention provides a method of inducing a cytokine in a cell. The method includes contacting the cell with an immunological regulator under conditions effective to induce (i.e., induce the synthesis or production of) at least one cytokine (either directly or indirectly), wherein the immunological regulator is selected from the group of MQPPPLP (SEQ ID NO:1); LQTPQPLLQVMMEPQGD (SEQ ID NO:2); DQPPDVEKPDLQPFQVQS (SEQ ID NO:3); LFFFLPVVNVLP (SEQ ID NO:4); DLEMPVLPVEPFPFV (SEQ ID NO:5); MPQNFYKLPQM (SEQ ID NO:6); VLEMKFPPPPQETVT (SEQ ID NO:7); LKPFPKLKVEVFPFP (SEQ ID NO:8); VVMEV (SEQ ID NO:9); SEQP (SEQ ID NO:10); DKE (SEQ ID NO:11); FPPPK (SEQ ID NO:12); DSQPPV (SEQ ID NO:13); DPPPPQS (SEQ ID NO:14); SEEMP (SEQ ID NO:15); KYKLQPE (SEQ ID NO:16); VLPPNVG (SEQ ID NO:17); VYPFTGPIPN (SEQ ID NO:18); SLPQNILPL (SEQ ID NO:19); TQTPVVVPPF (SEQ ID NO:20); LQPEIMGVPKVKETMVPK (SEQ ID NO:21); HKEMPFPKYPVEPFTESQ

(SEQ ID NO:22); SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23); SWMHQPP (SEQ ID NO:24); QPLPPTVMFP (SEQ ID NO:25); PQSVLS (SEQ ID NO:26); LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27); AFLLYQE (SEQ ID NO:28); RGPFPILV (SEQ ID NO:29); ATFNRYQDDHGEEILKSL (SEQ ID NO:30); FLLYQEPVLGPVR (SEQ ID NO:32); LNF (SEQ ID NO:33); and MHQPPQPLPPTVMFP (SEQ ID NO:34); an active analog thereof; and combinations thereof; with the proviso that the immunological regulator is not VESYVPLFP (SEQ ID NO:31). The cell can be in a cell culture, a tissue, an organ, or an organism. Hence, this method can be carried out *in vivo* or *in vitro*.

In another embodiment, there is provided a method for modulating an immune response in a cell. The method includes contacting the cell with an immunological regulator under conditions effective to induce at least one cytokine, wherein the immunological regulator is listed above. The cell can be in a cell culture, a tissue, an organ, or an organism. Hence, this method can be carried out *in vivo* or *in vitro*.

In yet another embodiment, there is provided a method for modulating an immune response in a patient. The method includes administering to the patient an immunological regulator under conditions effective to induce at least one cytokine, wherein the immunological regulator is listed above.

The immune response can be specific or nonspecific. Typically, one or more cytokines are directly induced using the polypeptides described herein, which then results in an upregulation or a downregulation of one or more other cytokines. Thus, using various combinations of polypeptides described herein, various cytokine profiles and immune responses can be produced, which may be specific or nonspecific. Examples of such immune responses include the interferon response and antibody production. As long as at least one cytokine level increases, whether it be increased as a result of direct inducement by one of the peptides described herein, or as a result of indirect inducement (e.g., through the interaction with another cytokine), a peptide is "active" as used herein.

In another embodiment, there is provided a method for modulating blood cell proliferation. The method includes contacting blood cells with a blood cell regulator selected from the group of colostrinin, a constituent peptide thereof,

an analog thereof, and combinations thereof, under conditions effective to change the number of blood cells. The blood cells can be in a cell culture or an organism. Hence, this method can be carried out *in vivo* or *in vitro*.

In still another embodiment, there is provided a method for modulating blood cell proliferation in a patient (preferably, a human patient). The method includes administering to the patient a blood cell regulator selected from the group of colostrinin, a constituent peptide thereof, an analog thereof, and combinations thereof, under conditions effective to change the number of blood cells.

The blood cells can be mammalian blood cells, such as human blood cells. Preferably, the blood cells are increased in number, although a decrease in number can also be desirable in certain situations such as leukemia, myelopathy, etc. More preferably, the blood cells are increased in number and differentiated. The blood cell regulator is preferably a constituent peptide of colostrinin.

In other embodiments, the invention provides the use of an immunological regulator or blood cell regulator in the manufacture of a medicament for use in the methods described herein.

The present invention also provides an immune-inducing composition that includes a pharmaceutical carrier and an active agent selected from the MQPPPLP (SEQ ID NO:1); LQTPQPLLQVMMEPQGD (SEQ ID NO:2); DQPPDVEKPDLQPFQVQS (SEQ ID NO:3); LFFFLPVVNVLP (SEQ ID NO:4); DLEMPVLPVEPFPFV (SEQ ID NO:5); MPQNFYKLPQM (SEQ ID NO:6); VLEMKFPPPPQETVT (SEQ ID NO:7); LKPFPKLKVEVFPFP (SEQ ID NO:8); VVMEV (SEQ ID NO:9); SEQP (SEQ ID NO:10); DKE (SEQ ID NO:11); FPPPK (SEQ ID NO:12); DSQPPV (SEQ ID NO:13); DPPPPQS (SEQ ID NO:14); SEEMP (SEQ ID NO:15); KYKLQPE (SEQ ID NO:16); VLPPNVG (SEQ ID NO:17); VYPFTGPIPN (SEQ ID NO:18); SLPQNILPL (SEQ ID NO:19); TQTPVVVPPF (SEQ ID NO:20); LQPEIMGVPKVKETMVPK (SEQ ID NO:21); HKEMPFPKYPVEPFTESQ (SEQ ID NO:22); SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23); SWMHQPP (SEQ ID NO:24); QPLPPTVMFP (SEQ ID NO:25); PQSVLS (SEQ ID NO:26); LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27); AFLLYQE (SEQ ID

NO:28); RGPFPILV (SEQ ID NO:29); ATFNRYQDDHGEEILKSL (SEQ ID NO:30); FLLYQEPVLGPVR (SEQ ID NO:32); LNF (SEQ ID NO:33); and MHQPPQPLPPTVMFP (SEQ ID NO:34); an active analog thereof; and combinations thereof; with the proviso that the immunological regulator is not VESYVPLFP (SEQ ID NO:31).

As used herein, "a" or "an" means one or more (or at least one), such that combinations of active agents (i.e., active immunological regulators or blood cell differentiation promoters), for example, can be used in the compositions and methods of the invention. Thus, a composition that includes "a" polypeptide refers to a composition that includes one or more polypeptides.

"Amino acid" is used herein to refer to a chemical compound with the general formula: NH_2---CRH---COOH, where R, the side chain, is H or an organic group. Where R is organic, R can vary and is either polar or nonpolar (i.e., hydrophobic). The amino acids of this invention can be naturally occurring or synthetic (often referred to as nonproteinogenic). As used herein, an organic group is a hydrocarbon group that is classified as an aliphatic group, a cyclic group or combination of aliphatic and cyclic groups. The term "aliphatic group" means a saturated or unsaturated linear or branched hydrocarbon group. This term is used to encompass alkyl, alkenyl, and alkynyl groups, for example. The term "cyclic group" means a closed ring hydrocarbon group that is classified as an alicyclic group, aromatic group, or heterocyclic group. The term "alicyclic group" means a cyclic hydrocarbon group having properties resembling those of aliphatic groups. The term "aromatic group" refers to mono- or polycyclic aromatic hydrocarbon groups. As used herein, an organic group can be substituted or unsubstituted.

The terms "polypeptide" and "peptide" are used interchangeably herein to refer to a polymer of amino acids. These terms do not connote a specific length of a polymer of amino acids. Thus, for example, the terms oligopeptide, protein, and enzyme are included within the definition of polypeptide or peptide, whether produced using recombinant techniques, chemical or enzymatic synthesis, or naturally occurring. This term also includes polypeptides that have been modified or derivatized, such as by glycosylation, acetylation,

phosphorylation, and the like.

The following abbreviations are used throughout the application:

A = Ala = Alanine	T = Thr = Threonine
V = Val = Valine	C = Cys = Cysteine
L = Leu = Leucine	Y = Tyr = Tyrosine
I = Ile = Isoleucine	N = Asn = Asparagine
P = Pro = Proline	Q = Gln = Glutamine
F = Phe = Phenylalanine	D = Asp = Aspartic Acid
W = Trp = Tryptophan	E = Glu = Glutamic Acid
M = Met = Methionine	K = Lys = Lysine
G = Gly = Glycine	R = Arg = Arginine
S = Ser = Serine	H = His = Histidine

Detailed Description of Preferred Embodiments of the Invention

The inventors have found that colostrinin, at least one constituent (i.e., component) peptide thereof, and/or at least one active analog thereof (e.g., a peptide having an N-terminal sequence equivalent to an N-terminal sequence of at least one of the colostrinin constituent peptides) can be used to induce at least one cytokine (e.g., TNF-α, IFN-γ, IL-1, IL-2, IL-4, IL-6, I-10, IL-12). The cytokine can be either directly or indirectly induced. This can result in the modulation of an immune response or blood cell proliferation or differentiation (preferably, the promotion of blood cell proliferation, and more preferably, the promotion of blood cell proliferation and differentiation) *in vitro* and *in vivo*, in animals (including mammals such as humans).

Such immunological regulators and blood cell regulators are referred to herein as "active agents." Significantly, such agents can be administered alone or in various combinations to a patient (e.g., animals including humans) as a medication or dietary (e.g., nutrient) supplement in a dose sufficient to modulate one or more immune responses throughout the patient's body, in a specific tissue site, or in a collection of tissue sites.

Many nonspecific and specific immune responses are associated with

leukocyte proliferation and differentiation. The overall immunological significance of the present invention can be, but is not limited to, the following: IFN-γ is a potent immunomodulater that is important for the development of the cytotoxic lymphocyte response (CTL). This immune response is considered to be very important in protecting humans and animals from a variety of bacterial, viral, parasitic, and fungal diseases. The fact that TNF-α is also induced is important because TNF-α is a major activator of macrophages, among other immune cells, which are important in host defense against infections. In addition, TNF-α has been shown to have activity against cancer, directly through its lytic activity and indirectly through macrophages. IL-10 is another important immune mediator that controls both IFN-γ and TNF-α production and action. Its production represent a negative feedback control for IFN-γ and TNF-α production. Another one of its hallmark activities is the control of antibody production during the humoral immune responses, which is certainly important in many types of infections. In addition to IL-10's immune activities, it also has been shown to play a role in the neuroendocrine system by modulating certain stress responses and immune responses. IL-10 has been shown to induce the production of corticotropin from pitutitary cells. Corticotropin works downstreanm in the hypothalmic adrenal axis to induce glucocortico steroids that are inherently immunomodulatory. Like IL-10, the IL-4 is important in the development of B cell responses, which are the mediators of the humoral immune response. Finally, the IL-12 is an important IFN-γ inducer. Taken together these findings suggest that colostrinin and its component peptides have the ability to modulate via cytokine induction a variety of host-defense mechanisms mediated by macrophages and lymphocytes at the cellular and humoral immune level as well as the neuroendocrine system.

Thus, the methods and compositions of the present invention can be utilized to control immunological and blood cell differentiating activity. The active agents described herein can be used individually, in various combinations, or combined with other previously known or newly invented pharmacological agents, such as antioxidants. They can be used as adjuvants for existing vaccinations as well.

In a preferred embodiment, the present invention provides a method for modulating an immune response. Whether it be *in vivo* or *in vitro*, this method involves monitoring the level of at least one cytokine, which can be done by known methods, such as disclosed by Inglot et al., Arch. Immunol. Ther. Exp., 44, 215-224 (1996); Blach-Olszewska et al., Arch. Immunol. Ther. Exp., 45, 43-47 (1997); Piasecki et al., Arch. Immunol. Ther. Exp., 45, 109-117 (1997); Hughes et al., Int. J. Immunopharmacol., 17, 857-863 (1995); and Mishell et al., Selected Methods in Cellular Immunology, W.H. Freeman, 1980. Specific *in vitro* methods are described in the Examples Section.

In another preferred embodiment, the present invention provides a method for modulating blood cell proliferation (preferably, proliferation and differentiation). Whether it be *in vivo* or *in vitro*, this method involves monitoring the level of increase or decrease in the number of blood cells bearing a specific phenotypic marker (for differentiation, the types of cells formed are evaluated), as disclosed by Kim et al., Clin. Lab. Haematol., 20, 21-29 (1998); Grunwald et al., Methods Mol. Biol., 119, 443-454 (1999); Villas et al., Cell. Vis., 5, 56-61 (1998); and Gratama et al., Cytometry, 33, 166-178 (1998). Specific *in vitro* methods are described in the Examples Section.

The peptides described herein may be used for the proliferation and/or differentiation of other types of cells as well.

Colostrinin is composed of peptides, the aggregate of which has a molecular weight range between about 5.8 to about 26 kiloDaltons (kDa) determined by polyacrylamide gel electrophoresis. It has a greater concentration of proline than any other amino acid. Ovine colostrinin has been found to have a molecular weight of about 18 kDa and includes three non-covalently linked subunits having a molecular weight of about 6 kDa and has about 22 wt-% proline. Ovine colostrinin has also been shown to contain the following number of residues per subunit: lysine - 2; histidine - 1; arginine - 0; aspartic acid - 2; threonine - 4; serine - 3; glutamic acid - 6; proline - 11; glycine - 2; alanine - 0; valine - 5; methionine - 2; isoleucine - 2; leucine - 6; tyrosine - 1; phenylalanine - 3; and cysteine - 0.

Colostrinin has been found to include a number of peptides ranging from

3 amino acids to 22 amino acids or more. These can be obtained by various known techniques, including isolation and purification involving eletrophoresis and synthetic techniques. The specific method of obtaining colostrinin and SEQ ID NO:31 is described in International Publication No. WO-A-98/14473. Using HPLC and Edelman Degradation, over 30 constituent peptides of colostrinin have been identified, which can be classified into several groups: (A) those of unknown precursor; (B) those having a β-casein homologue precursor; (C) those having a β-casein precursor; and (D) those having an annexin precursor. These peptides are described in International Patent Application PCT/GB00/02128, filed June 2, 2000, claiming priority to June 2, 1999, and can be synthesized according to the general method described in the Examples Section. These peptides (i.e., constituent peptides of colostrinin), which can be derived from colostrinin or chemically synthesized, include: MQPPPLP (SEQ ID NO:1); LQTPQPLLQVMMEPQGD (SEQ ID NO:2); DQPPDVEKPDLQPFQVQS (SEQ ID NO:3); LFFFLPVVNVLP (SEQ ID NO:4); DLEMPVLPVEPFPFV (SEQ ID NO:5); MPQNFYKLPQM (SEQ ID NO:6); VLEMKFPPPPQETVT (SEQ ID NO:7); LKPFPKLKVEVFPFP (SEQ ID NO:8); VVMEV (SEQ ID NO:9); SEQP (SEQ ID NO:10); DKE (SEQ ID NO:11); FPPPK (SEQ ID NO:12); DSQPPV (SEQ ID NO:13); DPPPPQS (SEQ ID NO:14); SEEMP (SEQ ID NO:15); KYKLQPE (SEQ ID NO:16); VLPPNVG (SEQ ID NO:17); VYPFTGPIPN (SEQ ID NO:18); SLPQNILPL (SEQ ID NO:19); TQTPVVVPPF (SEQ ID NO:20); LQPEIMGVPKVKETMVPK (SEQ ID NO:21); HKEMPFPKYPVEPFTESQ (SEQ ID NO:22); SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23); SWMHQPP (SEQ ID NO:24); QPLPPTVMFP (SEQ ID NO:25); PQSVLS (SEQ ID NO:26); LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27); AFLLYQE (SEQ ID NO:28); RGPFPILV (SEQ ID NO:29); ATFNRYQDDHGEEILKSL (SEQ ID NO:30); VESYVPLFP (SEQ ID NO:31); FLLYQEPVLGPVR (SEQ ID NO:32); LNF (SEQ ID NO:33); and MHQPPQPLPPTVMFP (SEQ ID NO:34). These can be classified as follows: (A) those of unknown precursor include SEQ ID NOs:2, 6, 7, 8, 10, 11, 14, and 33; (B) those having a β-casein homologue precursor include SEQ ID NOs:1, 3, 4, 5, 9, 12, 13, 15, 16, 17, and

31; (C) those having a β-casein precursor include SEQ ID NOs:18 (casein amino acids 74-83), 19 (casein amino acids 84-92), 20 (casein amino acids 93-102), 21 (casein amino acids 103-120), 22 (casein amino acids 121-138), 23 (casein amino acids 139-156), 24 (casein amino acids 157-163), 25 (casein amino acids 164-173), 26 (casein amino acids 174-179), 27 (casein amino acids 180-201), 28 (casein amino acids 202-208), 29 (casein amino acids 214-222), 32 (casein amino acids 203-214), and 34 (casein amino acids 159-173); and (D) those having an annexin precursor include SEQ ID NO:30 (annexin amino acids 203-220).

For certain embodiments, a preferred group of such peptides does not include SEQ ID NO:31. A more preferred group of such peptides includes: MQPPPLP (SEQ ID NO:1); LQTPQPLLQVMMEPQGD (SEQ ID NO:2); DQPPDVEKPDLQPFQVQS (SEQ ID NO:3); LFFFLPVVNVLP (SEQ ID NO:4); DLEMPVLPVEPFPFV (SEQ ID NO:5); MPQNFYKLPQM (SEQ ID NO:6); VLEMKFPPPPQETVT (SEQ ID NO:7); LKPFPKLKVEVFPFP (SEQ ID NO:8); VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

The polypeptides of SEQ ID NOs:1-34 can be in their free acid form or they can be amidated at the C-terminal carboxylate group. The present invention also includes analogs of the polypeptides of SEQ ID NOs:1-34, which includes polypeptides having structural similarity with SEQ ID NOs:1-34. These peptides can also form a part of a larger peptide. An "analog" of a polypeptide includes at least a portion of the polypeptide, wherein the portion contains deletions or additions of one or more contiguous or noncontiguous amino acids, or containing one or more amino acid substitutions. An "analog" can thus include additional amino acids at one or both of the terminii of the polypeptides listed above. Substitutes for an amino acid in the polypeptides of the invention are preferably conservative substitutions, which are selected from other members of the class to which the amino acid belongs. For example, it is well-known in the art of protein biochemistry that an amino acid belonging to a grouping of amino acids having a particular size or characteristic (such as

charge, hydrophobicity and hydrophilicity) can generally be substituted for another amino acid without substantially altering the structure of a polypeptide.

For the purposes of this invention, conservative amino acid substitutions are defined to result from exchange of amino acids residues from within one of the following classes of residues: Class I: Ala, Gly, Ser, Thr, and Pro (representing small aliphatic side chains and hydroxyl group side chains); Class II: Cys, Ser, Thr and Tyr (representing side chains including an -OH or -SH group); Class III: Glu, Asp, Asn and Gln (carboxyl group containing side chains): Class IV: His, Arg and Lys (representing basic side chains); Class V: Ile, Val, Leu, Phe and Met (representing hydrophobic side chains); and Class VI: Phe, Trp, Tyr and His (representing aromatic side chains). The classes also include related amino acids such as 3Hyp and 4Hyp in Class I; homocysteine in Class II; 2-aminoadipic acid, 2-aminopimelic acid, γ-carboxyglutamic acid, β-carboxyaspartic acid, and the corresponding amino acid amides in Class III; ornithine, homoarginine, N-methyl lysine, dimethyl lysine, trimethyl lysine, 2,3-diaminopropionic acid, 2,4-diaminobutyric acid, homoarginine, sarcosine and hydroxylysine in Class IV; substituted phenylalanines, norleucine, norvaline, 2-aminooctanoic acid, 2-aminoheptanoic acid, statine and β-valine in Class V; and naphthylalanines, substituted phenylalanines, tetrahydroisoquinoline-3-carboxylic acid, and halogenated tyrosines in Class VI.

Preferably, active analogs of colostrinin and its constituent peptides include polypeptides having a relatively large number of proline residues. Because proline is not a common amino acid, a "large number" preferably means that a polypeptide includes at least about 15% proline (by number), and more preferably at least about 20% proline (by number). Most preferably, active analogs include more proline residues than any other amino acid. For certain embodiments, preferred group of such active analogs does not include SEQ ID NO:31.

As stated above, active analogs of colostrinin and its constituent peptides include polypeptides having structural similarity. Structural similarity is generally determined by aligning the residues of the two amino acid sequences to optimize the number of identical amino acids along the lengths of their

sequences; gaps in either or both sequences are permitted in making the alignment in order to optimize the number of identical amino acids, although the amino acids in each sequence must nonetheless remain in their proper order. Preferably, two amino acid sequences are compared using the Blastp program, version 2.0.9, of the BLAST 2 search algorithm, available at http://www.ncbi.nlm.nih.gov/gorf/bl2.html. Preferably, the default values for all BLAST 2 search parameters are used, including matrix = BLOSUM62; open gap penalty = 11, extension gap penalty = 1, gap x_dropoff = 50, expect = 10, wordsize = 3, and filter on. In the comparison of two amino acid sequences using the BLAST search algorithm, structural similarity is referred to as "identity." Preferably, an active analog of colostrinin or its constituent peptides has a structural similarity to colostrinin or one or more of its constituent peptides (preferably, one of SEQ ID NOs:1-30) of at least about 70% identity, more preferably, at least about 80% identity, and most preferably, at least about 90% identity.

Colostrinin or any combination of its peptide components or active analogs thereof can be derived (preferably, isolated and purified) naturally such as by extraction from colostrum or can be synthetically constructed using known peptide polymerization techniques. For example, the peptides of the invention may be synthesized by the solid phase method using standard methods based on either t-butyloxycarbonyl (BOC) or 9-fluorenylmethoxy-carbonyl (FMOC) protecting groups. This methodology is described by G.B. Fields et al. in Synthetic Peptides: A User's Guide, W.M. Freeman & Company, New York, NY, pp. 77-183 (1992). Moreover, gene sequence encoding the colostrinin peptides or analogs thereof can be constructed by known techniques such as expression vectors or plasmids and transfected into suitable microorganisms that will express the DNA sequences thus preparing the peptide for later extraction from the medium in which the microorganism are grown. For example, U.S. Patent No. 5,595,887 describes methods of forming a variety of relatively small peptides through expression of a recombinant gene construct coding for a fusion protein which includes a binding protein and one or more copies of the desired target peptide. After expression, the fusion protein is isolated and cleaved using

chemical and/or enzymatic methods to produce the desired target peptide.

The peptides used in the methods of the present invention may be employed in a monovalent state (i.e., free peptide or a single peptide fragment coupled to a carrier molecule). The peptides may also be employed as conjugates having more than one (same or different) peptide fragment bound to a single carrier molecule. The carrier may be a biological carrier molecule (e.g., a glycosaminoglycan, a proteoglycan, albumin or the like) or a synthetic polymer (e.g., a polyalkyleneglycol or a synthetic chromatography support). Typically, ovalbumin, human serum albumin, other proteins, polyethylene glycol, or the like are employed as the carrier. Such modifications may increase the apparent affinity and/or change the stability of a peptide. The number of peptide fragments associated with or bound to each carrier can vary, but from about 4 to 8 peptides per carrier molecule are typically obtained under standard coupling conditions.

For instance, peptide/carrier molecule conjugates may be prepared by treating a mixture of peptides and carrier molecules with a coupling agent, such as a carbodiimide. The coupling agent may activate a carboxyl group on either the peptide or the carrier molecule so that the carboxyl group can react with a nucleophile (e.g., an amino or hydroxyl group) on the other member of the peptide/carrier molecule, resulting in the covalent linkage of the peptide and the carrier molecule. For example, conjugates of a peptide coupled to ovalbumin may be prepared by dissolving equal amounts of lyophilized peptide and ovalbumin in a small volume of water. In a second tube, 1-ethyl-3-(3-dimethylamino-propyl)-carbodiimide hydrochloride (EDC; ten times the amount of peptide) is dissolved in a small amount of water. The EDC solution was added to the peptide/ovalbumin mixture and allowed to react for a number of hours. The mixture may then dialyzed (e.g., into phosphate buffered saline) to obtain a purified solution of peptide/ovalbumin conjugate. Peptide/carrier molecule conjugates prepared by this method typically contain about 4 to 5 peptides per ovalbumin molecule.

The present invention also provides a composition that includes one or more active agents (i.e., colostrinin, at least one constituent peptide thereof, or

active analog thereof) of the invention and one or more carriers, preferably a pharmaceutically acceptable carrier. The methods of the invention include administering to, or applying to the skin of, a patient, preferably a mammal, and more preferably a human, a composition of the invention in an amount effective to produce the desired effect. The active agents of the present invention are formulated for enteral administration (oral, rectal, etc.) or parenteral administration (injection, internal pump, etc.). The administration can be via direct injection into tissue, interarterial injection, intervenous injection, or other internal administration procedures, such as through the use of an implanted pump, or via contacting the composition with a mucus membrane in a carrier designed to facilitate transmission of the composition across the mucus membrane such as a suppository, eye drops, inhaler, or other similar administration method or via oral administration in the form of a syrup, a liquid, a pill, capsule, gel coated tablet, or other similar oral administration method. The active agents can be incorporated into an adhesive plaster, a patch, a gum, and the like, or it can be encapsulated or incorporated into a bio-erodible matrix for controlled release.

The carriers for internal administration can be any carriers commonly used to facilitate the internal administration of compositions such as plasma, sterile saline solution, IV solutions or the like. Carriers for administration through mucus membranes can be any well-known in the art. Carriers for administration oral can be any carrier well-known in the art.

The formulations may be conveniently presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active agent into association with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active agent into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product into the desired formulations.

Formulations suitable for parenteral administration conveniently include a sterile aqueous preparation of the active agent, or dispersions of sterile powders of the active agent, which are preferably isotonic with the blood of the

recipient. Isotonic agents that can be included in the liquid preparation include sugars, buffers, and sodium chloride. Solutions of the active agent can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions of the active agent can be prepared in water, ethanol, a polyol (such as glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, glycerol esters, and mixtures thereof. The ultimate dosage form is sterile, fluid, and stable under the conditions of manufacture and storage. The necessary fluidity can be achieved, for example, by using liposomes, by employing the appropriate particle size in the case of dispersions, or by using surfactants. Sterilization of a liquid preparation can be achieved by any convenient method that preserves the bioactivity of the active agent, preferably by filter sterilization. Preferred methods for preparing powders include vacuum drying and freeze drying of the sterile injectible solutions. Subsequent microbial contamination can be prevented using various antimicrobial agents, for example, antibacterial, antiviral and antifungal agents including parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. Absorption of the active agents over a prolonged period can be achieved by including agents for delaying, for example, aluminum monostearate and gelatin.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as tablets, troches, capsules, lozenges, wafers, or cachets, each containing a predetermined amount of the active agent as a powder or granules, as liposomes containing the active agent, or as a solution or suspension in an aqueous liquor or non-aqueous liquid such as a syrup, an elixir, an emulsion, or a draught. The amount of active agent is such that the dosage level will be effective to produce the desired result in the subject.

Nasal spray formulations include purified aqueous solutions of the active agent with preservative agents and isotonic agents. Such formulations are preferably adjusted to a pH and isotonic state compatible with the nasal mucous membranes. Formulations for rectal or vaginal administration may be presented as a suppository with a suitable carrier such as cocoa butter, or hydrogenated fats or hydrogenated fatty carboxylic acids. Ophthalmic formulations are prepared by a similar method to the nasal spray, except that the pH and isotonic factors are

preferably adjusted to match that of the eye. Topical formulations include the active agent dissolved or suspended in one or more media such as mineral oil, DMSO, polyhydroxy alcohols, or other bases used for topical pharmaceutical formulations.

Useful dosages of the active agents can be determined by comparing their *in vitro* activity and the *in vivo* activity in animal models. Methods for extrapolation of effective dosages in mice, and other animals, to humans are known in the art; for example, see U.S. Patent No. 4,938,949.

The tablets, troches, pills, capsules, and the like may also contain one or more of the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, fructose, lactose or aspartame; and a natural or artificial flavoring agent. When the unit dosage form is a capsule, it may further contain a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac, or sugar and the like. A syrup or elixir may contain one or more of a sweetening agent, a preservative such as methyl- or propylparaben, an agent to retard crystallization of the sugar, an agent to increase the solubility of any other ingredient, such as a polyhydric alcohol, for example glycerol or sorbitol, a dye, and flavoring agent. The material used in preparing any unit dosage form is substantially nontoxic in the amounts employed. The active agent may be incorporated into sustained-release preparations and devices.

Examples

The invention will be further described by reference to the following detailed examples. The examples are meant to provide illustration and should not be construed as limiting the scope of the present invention. All peptides were dissolved in a balanced salt solution and/or DMSO.

Preparation of Peptides:

1. Wash pre-loaded resin with DMF (dimethylformamide), then drain completely.

2. Add 10 ml of 20% piperidine/DMF to resin. Shake for 5 minutes, then drain.

3. Add another 10 ml of 20% piperidine/DMF. Shake for 30 minutes.

4. Drain reaction vessel and wash resin with DMF four times. Then wash once with DCM (dichloromethanol). Check beads using the ninhydrin test - the beads should be blue.

5. The coupling step was carried out as follows:

   a. Prepare the following solution: 1 mmole Fmoc (i.e. fluorenylmethyloxycarbonyl) amino acid 2.1 ml of 0.45 M HBTU/HOBT (1 mmol) (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate/N-hydroxybenzotriazole-H_2O) 348 µl of DIEA (2 mmol) (diisopropylethylamine); and

   b. Add the solution to the resin and shake for a minimum of 30 minutes.

6. Drain reaction vessel and wash the resin again with DMF four times and with DCM once.

7. Perform the ninhydrin test: If positive (no colour) - proceed to step 2 and continue synthesis; If negative (blue colour) - return to step 5 and recouple the same Fmoc amino acid.

8. After the synthesis was complete, the peptide was cleaved from the resin with 5% H_2O, 5% phenol, 3% Thionisole, 3% EDT (ethanedithiol), 3% triisopropylsilane and 81% TFA for 2 hours.

9. After 2 hours, filter into cold MTBE (methyl t-butyl ether). The precipitated peptide was then washed twice with cold MTBE and dried under nitrogen gas.

10. The molecular weight of the synthesised peptides was checked by Matrix-Assisted Laser Desorption Time-of-Flight Mass Spectroscopy (LDMS), and the purity was checked by HPLC using a C-18, 300 Angstrom, 5 µm column.

Induction of Bood Cell Proliferation: The quantity of peripheral blood leukocyte (PBL) stimulation was determined by measuring the amount of ^{3}H-thymidine (1.0 to 2.0 μC thymidine/culture) incorporated into triplicate cultures (4 x 10^5 PBLs/culture) stimulated with colostrinin and its constituent peptides (CCP) for 72 hours. ^{3}H-thymidine was then added and allowed to incorporate for 24 hours. Staphylococcal enterotoxin A (SEA, also referred to as "super antigen"), a specific T cell mitogen, was used as a positive control and for comparative purposes. Colostrum and low and high iron containing baby formulas diluted 1:5 and 1:10 were also used in some experiments to determine the relative stimulatory activity of these products. Radioactivity was measured in a Matrix 9600 Direct Beta Counter. Six replicas of medium treated cultures were used to determine the mean background incorporated counts. The data is expressed as the mean ^{3}H-thymidine counts per minute (CPM) above background. Results of one out of a total of six experiments are shown below in Table 1.

It can be seen that colostrinin and its constituent peptides are excellent inducers of PBL proliferation. Active concentrations ranged from 100 μg/ml to 0.1 μg/ml. Nine peptides and colostrinin and colostrum were tested. Certain peptides appeared to have greater activity than others with the maximum increase in proliferative activity being roughly 10 times above background. It appears that with many of the peptides, the active range of proliferation induction was present since concentrations as low as 0.1 μg/ml still had potent activity. Some of the peptides had more activity than colostrinin alone. Another interesting finding is that colostrum appears to have roughly an equivalent amount of activity as colostrinin. SEA has the greatest activity and this is also not unexpected due to its classification as a super antigen. PBL proliferation is an important part of the immune response both for generating antigen reactive cells and induction of numerous modulating cytokines. In the newborn these processes are essential as a building block for development of an optimal immune response and provide a protective host defense barrier against diseases associated with the neonatal gut.

Table 1 - Effect of CCP on Fresh Human Leukocyte Cultures

Peptide	Peptide Conc. µg/ml	Slide No.	Microscope 3 plus to 0	Mitogenic Activity CPM
SEQ ID NO:1	100	1	+++	1259
	10	2	++	4556
	1.0	3	+	4829
	0.1	4	+/-	3339
SEQ ID NO:7	100	5	++	1383
	10	6	+	3478
	1.0	7	+/-	2290
	0.1	8	-	584
SEQ ID NO:8	100		-	2039
	10	9	-	1810
	1.0	10	+++	1527
	0.1	11	++	2177
SEQ ID NO:3	100	ND	-	469
	10	ND	-	819
	1.0	ND	-	3323
	0.1	ND	-	86
SEQ ID NO:2	100	ND	-	29
	10	12	-	2989
	1.0	13	++	4809
	0.1	14	+/-	3578
SEQ ID NO:4	100	15	+	2667
	10	16	+	4915
	1.0	ND	-	4050
	0.1	ND	-	3523
SEQ ID NO:5	100	ND	-	1762
	10	ND	-	3304
	1.0	ND	-	1938
	0.1	ND	-	1630
SEQ ID NO:6	100	ND	-	748
	10	ND	-	3069
	1.0	ND	-	1375
	0.1	ND	-	1171
SEQ ID NO:31	100	23	+++	2039
	10	24	++	200
	1.0	25	+	901
	0.1	26	-	1875
Colostrinin	10	20	++	2470
	1.0	21	+	1614
	0.1	22	-	2535
Colostrum	100	17	++	1094
	10	18	-	2991

	1.0 0.1	19 ND	- -	3320 2717
SEA	.02	ND	++++	6554
Control		27	-	461

ND = not done
+++ = strong induction of lymphoblasts and/or monocytes
++ = medium induction of lymphoblasts and/or monocytes
+ = low induction of lymphoblasts and/or monocytes
+/- = some induction of lymphoblasts and/or monocytes
- = same as control
Mitogenic Activity = CPM above control as determined by 24-hour ^{3}H-thymidine incorporation.

Cytokine studies: Colostrinin has previously been shown in the literature to induce IFN-γ and TNF-α, as has Val-Glu-Ser-Tyr-Val-Pro-Leu-Phe-Pro (SEQ ID NO:31), which is disclosed in International Publication No. WO-A-98/1447. Thus, studies were done to investigate the individual peptides.

Cytokine concentrations were also determined from cells following 72 hours of incubation with concentrations of colistrinin and its constituent peptides (CCP) ranging from 100 to 0.1 μg/ml, and colostrum and high- or low-iron baby formula (Enfamil) at various dilutions. Supernatant fluids were then subjected to enzyme-linked immunosorbent assay (ELISA) for the following commercially available cytokines: interferon-gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukin (IL)-4, IL-6, IL-10, and IL-12.

Table 2 represents the results of approximately 250 single assays. More specifically, in these studies it was found that many of the peptides including colostrinin induced IFN-γ and that the data corresponds with ^{3}H-thymidine incorporation (Tables 1 and 3). Interestingly the maximum cytokine inducing activity of many of the peptides was not diluted out until the 1.0 or 0.1 μg/ml concentrations of peptide were used (Shaded numbers in Table 2), or in the case of IFN-γ and TNF-α induction by SEQ ID NO:31 and SEQ ID NO:1, 0.1 μg/ml rather than higher concentrations. This finding may be consistent with a phasic response like those of hormones or of toxicity present in higher concentrations.

The ability to induce IFN-γ by some of the peptides decayed over time.

For example, SEQ ID NO:31 at 0.1 μg/ml at the beginning of the studies induced 324 pg IFN–γ/ml and in the last experiments induced no detectable levels. Although the peptides lost the IFN-γ inducing activity over a period of four months when stored in solution, some of the peptides were still able to induce TNF-α, IL-6, and IL-12, but the levels produced were somewhat lower than in the earlier studies. In contrast, induction of TNF-α and IL-10 by colostrinin and colostrum was still very high at this time. Thus, the complexed peptides making up colostrinin and colostrum may be more stable and/or combinations of peptides in colostrinin and colostrum may be more potent. Additional factors that may account for the variations of the peptides in these studies include: 1) natural variations in the immune state of the individuals donating the leukocytes, 2) the possibility that aggregation occurred in samples stored in PBS, thus reducing in effective number of molecules able to react, and 3) the possibility that the individual peptides may be subject to oxidative damage or some other inactivating process. The fact that the peptide, SEQ ID NO:8, which still induced IFN-γ in the last experiment (Example 3) was stored in 33% DMSO suggests an oxidative process or aggregation problem may be responsible for loss, or reduction of inducing activity in peptide samples stored in phosphate buffered saline (PBS). However, the samples in PBS appeared to be in solution at the time of the induction experiments.

Table 2. Cytokines induced in human leukocyte cultures stimulated with CCP, colostrum or commercial milk formulas.

PEPTIDE (Exp. #)	PEPTIDE CONCENTRATION (mg/ml)	IFN γ (pg/ml)	TNF-α (pg/ml)	IL-10 (pg/ml)
Example 1				
SEQ ID NO:1	100	54	478	168
	10	526	>1000	940
	1	584	>1000	1070
	0.1	236	722	696
SEQ ID NO:7	100	317	>1000	998
	10	409	>1000	1134
SEQ ID NO:8	100	419	>1000	860
	10	775	>1000	1643
	1	877	>1000	2223
	0.1	642	>1000	1350
SEQ ID NO:3	1	809	>1000	1611
	0.1	206	802	611
SEQ ID NO:2	100	372	>1000	754
	10	410	>1000	1063
	1	826	>1000	2092
	0.1	259	>1000	596
SEQ ID NO:4	10	794	>1000	1494
	1	723	>1000	1765
SEQ ID NO:5	100	559	>1000	756
	10	626	>1000	1158
SEQ ID NO:6	100	91	718	302
	10	621	>1000	1203
SEQ ID NO:31	100	371	804	4234
	10	107	370	1834
	1	118	651	242
	0.1	324	>1000	356

Colistrinin	10	888	>1000	1515
	1	878	>1000	1150
	0.1	156	760	451
Raw Colostrum	100	807	>1000	857
	10	530	>1000	1074
	1	934	>1000	1645
	0.1	192	848	391
Control		4	52	0
SEA		902	>1000	4676

Example 2

SEQ ID NO:18	100	4	24	36
SEQ ID NO:19	10	6	65	76
	1	463	>1000	502
SEQ ID NO:20	100	9	30	21
	10	31	118	101
SEQ ID NO:22	100	535	>1000	524
	10	539	985	409
	1	649	>1000	460
	0.1	147	636	207
SEQ ID NO:1	100	9	92	108
	10	14	99	129
	1	287	728	292
	0.1	576	>1000	397
SEQ ID NO:7	100	762.9	>1000	639
SEQ ID NO:2	100	980	>1000	646
	10	828	>1000	651
	1	914	>1000	1093
	0.1	281	685	348

	Enfamil	1:5	101	305	24
	Low Iron	1:10	167	406	443
5	Enfamil	1:5	24	528	136
	with Iron	1:10	10	320	702
	Control		7	248	180
10	SEA		901	>1000	2806
	Example 3				
15	SEQ ID NO:1	100	6	110	0
		10	4	ND	ND
	SEQ ID NO:7	1	9	57	0
		0.1	6	ND	ND
20					
	SEQ ID NO:8	10	8	20	0
		1	288	ND	ND
	SEQ ID NO:5	100	3	0	0
25					
	Raw	100	5	11	0
	Colostrum	10	15	520	569
		1	0	ND	ND
		0.1	0	ND	ND
30					
	Colostrinin	10	0	>1000	3662
		1	18	910	1839
		0.1	1	ND	ND
35	SEQ ID NO:31	10	0	11	0
		1	0	90	0
		0.1	0	ND	ND
	SEQ ID NO:22	100	0	120	77.6
40		10	0	60	0
		1	0	7	0
		0.1	0	ND	ND

Enfamil Low Iron	1:5	25	339	51
Enfamil with Iron	1:5	0	452	51
Control		0	0	0
SEA		700	>1000	2971
Example 4				
SEQ ID NO:1	100	0	73.3	0
SEQ ID NO:2	1	0	0	0
Colostrinin	10	0	1790	6.9
	1	0	1813	0
	0.1	ND	ND	ND
Raw Colostrum	100	0	1834	4.0
	10	0	31.2	0
	1	ND	ND	ND
Control		0	28.4	0
SEA		3.5	1927	13.4

Table 2. (cont.) Cytokines induced in human leukocyte cultures stimulated with CCP, colostrum or commercial milk formulas.

PEPTIDE (Exp. #)	PEPTIDE CONCENTRATION (mg/ml)	IL-4 (pg/ml)	IL-6 (pg/ml)	IL-12 (pg/ml)
Example 1				
SEQ ID NO:1	100	0	235.4	0
	10	0	934.8	0
	1	0	675.3	0
	0.1	0	497.1	0
SEQ ID NO:7	100	0	291.3	0
	10	0	645.4	0
SEQ ID NO:8	100	0	1076	0
	10	0	1024	0
	1	0	1013	0
	0.1	0	533.6	0
SEQ ID NO:3	1	0	620.5	0
	0.1	0	107	0
SEQ ID NO:2	100	0	258.6	0
	10	0	551.3	0
	1	0	1205	0
	0.1	0	325	0
SEQ ID NO:4	10	0	1718	0
	1	0	744.4	0
SEQ ID NO:5	100	0	98.2	0
	10	0	750	0
SEQ ID NO:6	100	0	63.3	0
	10	0	864.5	0

	SEQ ID NO:31	100	1.4	1489	0
		10	0	836.3	0
		1	0.4	489.9	0
		0.1	2.4	1635	0
	Colostrinin	10	0	1832	0
		1	1.9	1915	0
		0.1	0.4	430.1	0
	Raw Colostrum	100	0	1879	0
		10	0	602.2	0
		1	0	1055	0
		0.1	5.0	187.2	0
	Control		0	13.5	0
	SEA		4	1704	0
	Example 2				
	SEQ ID NO:18	100	0	142.4	0
	SEQ ID NO:19	10	0	549.7	0
		1	33.8	1552	0
	SEQ ID NO:20	100	0	50	0
		10	0.4	105.9	0
	SEQ ID NO:22	100	41.5	808.6	0
		10	32.7	503.2	0
		1	30.1	1005	0
		0.1	17.8	396.4	0
	SEQ ID NO:1	100	0	1471	0
		10	3.5	96.5	5.7
		1	26.6	626.6	0
		0.1	47.6	1385	0
	SEQ ID NO:7	100	24.5	1546	0
	SEQ ID NO:2	100	22.5	1292	33.5
		10	19.9	1516	0

		1	10.1	1886	9.9
		0.1	29.1	478.3	2.2
	Enfamil	1:5	0.9	1757	0
5	Low Iron	1:10	4.0	1958	0
	Enfamil	1:5	0	1909	0
	with Iron	1:10	0	ND	0
10	Control		0	183.5	0
	SEA		62.5	1769	54.8
15	**Example 3**				
	SEQ ID NO:1	100	0	942.5	0
		10	ND	ND	ND
	SEQ ID NO:7	1	0	32.9	0
20		0.1	ND	ND	ND
	SEQ ID NO:8	10	0	18.5	4.0
		1	ND	ND	ND
25	SEQ ID NO:5	100	0	0	0
	Raw	100	0	0	0
	Colostrum	10	0	1853	1.6
		1	ND	ND	ND
30		0.1	ND	ND	ND
	Colostrinin	10	0	2009	17.6
		1	0	1861	7.5
		0.1	ND	ND	ND
35					
	SEQ ID NO:31	10	0	16.8	18.7
		1	0	722.9	0
		0.1	ND	ND	ND
40	SEQ ID NO:22	100	6.0	1630	0
		10	0	46.7	0
		1	0	0	0

	0.1	ND	ND	ND
Enfamil Low Iron	1:5	0	1913	0
Enfamil with Iron	1:5	0.4	1953	0
Control		0	0	0
SEA		16.8	866.2	0

*SEQ ID NOs:1-8 and 31, Raw Colostrum, and Colostrinin were reconstituted on the same day.
*SEQ ID NOs:18, 19, 20, and 22 were reconstituted on the same day.

The relative abilities of the various peptides to induce cytokines are shown in Table 3. The peptides were ranked according to their abilities to induce the indicated cytokine by first comparing the raw numbers at the 0.1 μg/ml concentration followed by 1.0 μg/ml concentrations and then higher concentrations, i.e., 10 and 100 μg/ml. It can be noted that SEQ ID NOs:1, 8, 3, 2, and 31 were the best overall inducers in almost all cytokine and blood cell proliferation experiments. Peptides SEQ ID NOs:7, 4, and 5 were generally less effective as inducers. Colistrinin and colostrum ranked generally in the middle, however, only 1:5 and 1:10 dilutions of colostrum were used, thus actual comparison are not accurate since specific protein species present and their concentrations were not determined for colostrum. It is important to note, however, that colostrum contained substances that could induce cytokines in a similar fashion to colostrinin and its component peptides.

When the colostrinin constituent peptides having a β-casein precursor (SEQ ID NOs: 18, 19, 20, and 22) were compared to the initially tested SEQ ID NOs:1-8 and 31, the latter were better inducers. SEQ ID NO:22 was generally the best inducer of those peptides having a β-casein precursor. It was also found that Enfamil low iron baby formula induced higher levels of cytokines than the Enfamil high iron formula.

Table 3. Relative abilities of the various peptides to induce cytokines and proliferation

Rank	Ex. 1 IFN-γ	Ex. 2 IFN-γ	Ex. 1 Micro. Resp.	Ex. 1 Prolif. Resp.	Ex. 1 TNF-α	Ex. 2 TNF-α	Ex. 1 IL-10
1	SEQ ID NO:8	SEQ ID NO:1	SEQ ID NO:8	SEQ ID NO:2	SEQ ID NO:2**	SEQ ID NO:2	SEQ ID NO:8
2	SEQ ID NO:31	SEQ ID NO:2	SEQ ID NO:2	SEQ ID NO:1	SEQ ID NO:8	SEQ ID NO:1	SEQ ID NO:1
3	SEQ ID NO:2	SEQ ID NO:7	SEQ ID NO:31	SEQ ID NO:4	SEQ ID NO:31	SEQ ID NO:7	SEQ ID NO:3
4	SEQ ID NO:1	SEQ ID NO:22	SEQ ID NO:1	Colostrum	Colostrum	SEQ ID NO:22	SEQ ID NO:2
5	SEQ ID NO:3	SEQ ID NO:19	SEQ ID NO:7	Colostrinin	Colostrinin	SEQ ID NO:19	Colostrinin
6	Colistrinin	SEQ ID NO:20	Colostrinin	SEQ ID NO:8	SEQ ID NO:3	SEQ ID NO:20	Colostrum
7	Colustrum	SEQ ID NO:18	Colostrum	SEQ ID NO:31	SEQ ID NO:1	SEQ ID NO:18	SEQ ID NO:31
8	SEQ ID NO:4		SEQ ID NO:3	SEQ ID NO:5	SEQ ID NO:5		SEQ ID NO:4
9	SEQ ID NO:5		SEQ ID NO:4	SEQ ID NO:6	SEQ ID NO:7	Low Enfamil	SEQ ID NO:7
9	SEQ ID NO:6		SEQ ID NO:5	SEQ ID NO:7	SEQ ID NO:4	High Enfamil	SEQ ID NO:5
10	SEQ ID NO:7		SEQ ID NO:6	SEQ ID NO:3	SEQ ID NO:6		SEQ ID NO:6

* SEQ ID NO:7 < 2 fold difference in titer
** All good inducers
*** No difference in titer

Table 3. (Cont.) Relative abilities of the various peptides to induce cytokines and proliferation

Rank	Ex. 2 IL-10	Ex. 1 IL-4	Ex. 2 IL-4	Ex. 1 IL-6	Ex. 2 IL-6	Ex. 1 IL-12	Ex. 2 IL-12
1	SEQ ID NO:2	Colostrum	SEQ ID NO:1	SEQ ID NO:31	Control	All neg.	SEQ ID NO:2
2	SEQ ID NO:7	Colostrinin	SEQ ID NO:2	SEQ ID NO:8			SEQ ID NO:1
3	SEQ ID NO:1	SEQ ID NO:31	SEQ ID NO:22	SEQ ID NO:1			
4	SEQ ID NO:19		SEQ ID NO:19	Colostrinin			
5	SEQ ID NO:22		SEQ ID NO:7	SEQ ID NO:2			
6	SEQ ID NO:20		Low Enfamil	Colostrum			
7	SEQ ID NO:18			SEQ ID NO:3			
8				SEQ ID NO:4			
9	Low Enfamil			SEQ ID NO:6			
9	High Enfamil			SEQ ID NO:5			
10				SEQ ID NO:7			

* SEQ ID NO:7 < 2 fold difference in titer
** All good inducers
*** No difference in titer

Although the invention has been disclosed with reference to its preferred embodiments, from reading this description those of skill in the art may appreciate changes and modification that may be made which do not depart from the scope and spirit of the invention as described above and claimed hereafter. All references, patents, and patent applications cited herein are incorporated herein by reference in their entirety as if individually incorporated.

Sequence Listing Free Text

The following are all synthetic peptide sequences.

SEQ ID NO:1	MQPPPLP
SEQ ID NO:2	LQTPQPLLQVMMEPQGD
SEQ ID NO:3	DQPPDVEKPDLQPFQVQS
SEQ ID NO:4	LFFFLPVVNVLP
SEQ ID NO:5	DLEMPVLPVEPFPFV
SEQ ID NO:6	MPQNFYKLPQM
SEQ ID NO:7	VLEMKFPPPPQETVT
SEQ ID NO:8	LKPFPKLKVEVFPFP
SEQ ID NO:9	VVMEV
SEQ ID NO:10	SEQP
SEQ ID NO:11	DKE
SEQ ID NO:12	FPPPK
SEQ ID NO:13	DSQPPV
SEQ ID NO:14	DPPPPQS
SEQ ID NO:15	SEEMP
SEQ ID NO:16	KYKLQPE
SEQ ID NO:17	VLPPNVG
SEQ ID NO:18	VYPFTGPIPN
SEQ ID NO:19	SLPQNILPL
SEQ ID NO:20	TQTPVVVPPF
SEQ ID NO:21	LQPEIMGVPKVKETMVPK

SEQ ID NO:22	HKEMPFPKYPVEPFTESQ
SEQ ID NO:23	SLTLTDVEKLHLPLPLVQ
SEQ ID NO:24	SWMHQPP
SEQ ID NO:25	QPLPPTVMFP
SEQ ID NO:26	PQSVLS
SEQ ID NO:27	LSQPKVLPVPQKAVPQRDMPIQ
SEQ ID NO:28	AFLLYQE
SEQ ID NO:29	RGPFPILV
SEQ ID NO:30	ATFNRYQDDHGEEILKSL
SEQ ID NO:31	VESYVPLFP
SEQ ID NO:32	FLLYQEPVLGPVR
SEQ ID NO:33	LNF
SEQ ID NO:34	MHQPPQPLPPTVMFP

We claim:

1. A method of inducing a cytokine in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is selected from the group of MQPPPLP (SEQ ID NO;1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, with the proviso that the immunological regulator is not VESYVPLFP (SEQ ID NO:31).

2. The method of claim 1 wherein the cell is present in a cell culture, a tissue, an organ, or an organism.

3. The method of claim 1 wherein the cell is a mammalian cell.

4. The method of claim 3 wherein the cell is a human cell.

5. The method of claim 1 wherein the immunological regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD

(SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8),VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

6. A method for modulating an immune response in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, with the proviso that the immunological regulator is not VESYVPLFP (SEQ ID NO:31).

7. The method of claim 6 wherein the cell is present in a cell culture, a tissue, an organ, or an organism.

8. The method of claim 6 wherein the cell is a mammalian cell.

9. The method of claim 8 wherein the cell is a human cell.

10. The method of claim 6 wherein the immunological regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

11. A method for modulating an immune response in a patient, the method comprising administering to the patient an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and

MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, with the proviso that the immunological regulator is not VESYVPLFP (SEQ ID NO:31).

12. The method of claim 11 wherein the immunological regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

13. The method of claim 11 wherein the immunological regulator is administered as part of a dietary supplement.

14. The method of claim 11 wherein the immunological regulator is administered topically.

15. The method of claim 11 wherein the patient is an animal.

16. The method of claim 15 wherein the patient is a human.

17. The method of claim 11 wherein the immune response is a specific immune response.

18. The method of claim 11 wherein the immune response is a nonspecific immune response.

19. The method of claim 11 wherein the immune response is the interferon response or antibody production.

20. A method for modulating blood cell proliferation, the method comprising contacting blood cells with a blood cell regulator selected from the group of colostrinin, a constituent peptide thereof, an analog thereof, and combinations thereof, under conditions effective to change the number of blood cells.

21. The method of claim 20 wherein the blood cells are present in a cell culture or an organism.

22. The method of claim 20 wherein the blood cells are mammalian cells.

23. The method of claim 22 wherein the blood cells are human cells.

24. The method of claim 22 wherein the blood cells are increased in number.

25. The method of claim 24 wherein the blood cells are differentiated.

26. The method of claim 22 wherein the blood cell regulator is a constituent peptide of colostrinin.

27. The method of claim 26 wherein the blood cell regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP

(SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof.

28. The method of claim 27 wherein the blood cell regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

29. A method for modulating blood cell proliferation in a patient, the method comprising administering to the patient a blood cell regulator selected from the group of colostrinin, a constituent peptide thereof, an analog thereof, and combinations thereof, under conditions effective to change the number of blood cells.

30. The method of claim 29 wherein the patient is a human.

31. The method of claim 29 wherein the blood cells are increased in number.

32. The method of claim 31 wherein the blood cells are differentiated.

33. The method of claim 29 wherein the blood cell regulator is a constituent peptide of colostrinin.

34. The method of claim 33 wherein the blood cell regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof.

35. The method of claim 34 wherein the blood cell regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8),VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

36. A cytokine-inducing composition comprising a pharmaceutical carrier and an active agent selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV

(SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, with the proviso that the active agent is not VESYVPLFP (SEQ ID NO:31).

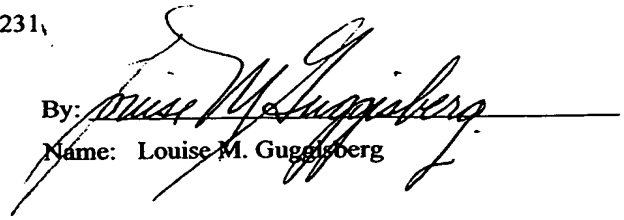
USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

Abstract of the Disclosure

The present invention discloses a use of colostrinin, a constituent peptide thereof, and/or an analog thereof as an immunological regulator and as a blood cell regulator in animals including humans.

Express Mail" mailing label number: EL518336573US Date of Deposit: 17 August 2000

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, ATTN: Box Patent Application, Washington, D.C. 20231.

By: 

Name: Louise M. Guggisberg

SEQUENCE LISTING

<110> STANTON, G. John
HUGHES, Thomas K.
BOLDOGH, Istvan
GEORGIADES, Jerzy

<120> USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF
FOR INDUCING CYTOKINES

<130> 265.00230101

<140> Unassigned
<141> 2000-08-17

<150> 60/149,311
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Pro Lys

<210> 22
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1 5

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Ser Leu

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1 5 10 15

Exhibit A

Receipt is hereby acknowledged for the following in the U.S. Patent and Trademark Office:

Applicant(s): Stanton et al.
Serial No.: 09/641,801 Confirmation No.: 5388
Filed: August 17, 2000
Title: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES
Enclosed: An Information Disclosure Statement (2 pgs); copy of an International Search Report; copies of 2 U.S. applications; 1449 forms (5 pgs); and copies of 69 documents cited on the 1449 forms; Preliminary Amendment with Appendix A (22 pgs.); and transmittal document (in triplicate).

Mailed: June 11, 2001
Docket No.: 265.0023 0101

AMM:GLL:lmg

Receipt is hereby acknowledged for the following in the U.S. Patent and Trademark Office:

Applicant(s): Stanton et al.
Serial No.: 09/641,801 Confirmation No.: 5388
Filed: August 17, 2000
Title: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES
Enclosed: An Information Disclosure Statement (2 pgs); copy of an International Search Report; copies of 2 U.S. applications; 1449 forms (5 pgs); and copies of 69 documents cited on the 1449 forms; Preliminary Amendment with Appendix A (22 pgs.); and transmittal document (in triplicate).

Mailed: June 11, 2001
Docket No.: 265.0023 0101

AMM:GLL:lmg

PATENT
Docket No. 265.0023 0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Stanton et al.	Group Art Unit:	1645
Serial No.:	09/641,801	Examiner:	unknown
Confirmation No.:	5388		
Filed:	August 17, 2000		

For: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington D.C. 20231

Sir:

Prior to taking up the above-identified patent application for examination, please enter the following amendments.

In The Specification

Please replace the paragraph at page 8, line 32 to page 10, line 9, with the following rewritten paragraph. Per 37 C.F.R §1.121, this paragraph is also shown in Appendix A, page A1, with notations to indicate the changes made.

Colostrinin has been found to include a number of peptides ranging from 3 amino acids to 22 amino acids or more. These can be obtained by various known techniques, including isolation and purification involving eletrophoresis and synthetic techniques. The specific method of obtaining colostrinin and SEQ ID NO:31 is described in International Publication No. WO-A-98/14473. Using HPLC and Edelman Degradation, over 30 constituent peptides of colostrinin have been identified, which can be classified into several groups: (A) those of unknown precursor; (B) those having a β-casein homologue precursor; (C) those having a β-casein precursor; and (D) those having an annexin precursor. These

peptides are described in International Patent Publication No. WO 00/75173, filed June 2, 2000, claiming priority to June 2, 1999, and can be synthesized according to the general method described in the Examples Section. These peptides (i.e., constituent peptides of colostrinin), which can be derived from colostrinin or chemically synthesized, include: MQPPPLP (SEQ ID NO:1); LQTPQPLLQVMMEPQGD (SEQ ID NO:2); DQPPDVEKPDLQPFQVQS (SEQ ID NO:3); LFFFLPVVNVLP (SEQ ID NO:4); DLEMPVLPVEPFPFV (SEQ ID NO:5); MPQNFYKLPQM (SEQ ID NO:6); VLEMKFPPPPQETVT (SEQ ID NO:7); LKPFPKLKVEVFPFP (SEQ ID NO:8); VVMEV (SEQ ID NO:9); SEQP (SEQ ID NO:10); DKE (SEQ ID NO:11); FPPPK (SEQ ID NO:12); DSQPPV (SEQ ID NO:13); DPPPPQS (SEQ ID NO:14); SEEMP (SEQ ID NO:15); KYKLQPE (SEQ ID NO:16); VLPPNVG (SEQ ID NO:17); VYPFTGPIPN (SEQ ID NO:18); SLPQNILPL (SEQ ID NO:19); TQTPVVVPPF (SEQ ID NO:20); LQPEIMGVPKVKETMVPK (SEQ ID NO:21); HKEMPFPKYPVEPFTESQ (SEQ ID NO:22); SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23); SWMHQPP (SEQ ID NO:24); QPLPPTVMFP (SEQ ID NO:25); PQSVLS (SEQ ID NO:26); LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27); AFLLYQE (SEQ ID NO:28); RGPFPILV (SEQ ID NO:29); ATFNRYQDDHGEEILKSL (SEQ ID NO:30); VESYVPLFP (SEQ ID NO:31); FLLYQEPVLGPVR (SEQ ID NO:32); LNF (SEQ ID NO:33); and MHQPPQPLPPTVMFP (SEQ ID NO:34). These can be classified as follows: (A) those of unknown precursor include SEQ ID NOs:2, 6, 7, 8, 10, 11, 14, and 33; (B) those having a β-casein homologue precursor include SEQ ID NOs:1, 3, 4, 5, 9, 12, 13, 15, 16, 17, and 31; (C) those having a β-casein precursor include SEQ ID NOs:18 (casein amino acids 74-83), 19 (casein amino acids 84-92), 20 (casein amino acids 93-102), 21 (casein amino acids 103-120), 22 (casein amino acids 121-138), 23 (casein amino acids 139-156), 24 (casein amino acids 157-163), 25 (casein amino acids 164-173), 26 (casein amino

acids 174-179), 27 (casein amino acids 180-201), 28 (casein amino acids 202-208), 29 (casein amino acids 214-222), 32 (casein amino acids 203-214), and 34 (casein amino acids 159-173); and (D) those having an annexin precursor include SEQ ID NO:30 (annexin amino acids 203-220).

Please replace the paragraph at page 20, line 38 to line 41, with the following rewritten paragraph. Per 37 C.F.R §1.121, this paragraph is also shown in Appendix A, page A3, with notations to indicate the changes made.

Cytokine studies: Colostrinin has previously been shown in the literature to induce IFN-γ and TNF-α, as has Val-Glu-Ser-Tyr-Val-Pro-Leu-Phe-Pro (SEQ ID NO:31), which is disclosed in International Publication No. WO-A-98/14473. Thus, studies were done to investigate the individual peptides.

Please replace the paragraph at page 26, line 3 to page 29, line 16, with the following rewritten paragraph. Per 37 C.F.R §1.121, this paragraph is also shown in Appendix A, page A4, with notations to indicate the changes made.

Table 2. (cont.) Cytokines induced in human leukocyte cultures stimulated with CCP, colostrum or commercial milk formulas.

PEPTIDE (Exp. #)	PEPTIDE CONCENTRATION (mg/ml)	IL-4 (pg/ml)	IL-6 (pg/ml)	IL-12 (pg/ml)
Example 1				
SEQ ID NO:1	100	0	235.4	0
	10	0	934.8	0
	1	0	675.3	0
	0.1	0	497.1	0
SEQ ID NO:7	100	0	291.3	0
	10	0	645.4	0
SEQ ID NO:8	100	0	1076	0
	10	0	1024	0
	1	0	1013	0
	0.1	0	533.6	0
SEQ ID NO:3	1	0	620.5	0
	0.1	0	107	0
SEQ ID NO:2	100	0	258.6	0
	10	0	551.3	0
	1	0	1205	0
	0.1	0	325	0

SEQ ID NO:4	10	0	1718	0
	1	0	744.4	0
SEQ ID NO:5	100	0	98.2	0
	10	0	750	0
SEQ ID NO:6	100	0	63.3	0
	10	0	864.5	0
SEQ ID NO:31	100	1.4	1489	0
	10	0	836.3	0
	1	0.4	489.9	0
	0.1	2.4	1635	0
Colostrinin	10	0	1832	0
	1	1.9	1915	0
	0.1	0.4	430.1	0
Raw Colostrum	100	0	1879	0
	10	0	602.2	0
	1	0	1055	0
	0.1	5.0	187.2	0
Control		0	13.5	0
SEA		4	1704	0

Example 2

SEQ ID NO:18	100	0		0
SEQ ID NO:19	10	0		0
	1	33.8		0
SEQ ID NO:20	100	0		0

	10	0.4		0
SEQ ID NO:22	100	41.5		0
	10	32.7		0
	1	30.1		0
	0.1	17.8		0
SEQ ID NO:1	100	0		0
	10	3.5		5.7
	1	26.6		0
	0.1	47.6		0
SEQ ID NO:7	100	24.5		0
SEQ ID NO:2	100	22.5		33.5
	10	19.9		0
	1	10.1		9.9
	0.1	29.1		2.2
Enfamil	1:5	0.9		0
Low Iron	1:10	4.0		0
Enfamil	1:5	0		0
with Iron	1:10	0		0
Control		0		0
SEA		62.5		54.8
Example 3				
SEQ ID NO:1	100	0	942.5	0
	10	ND	ND	ND
SEQ ID NO:7	1	0	32.9	0
	0.1	ND	ND	ND

SEQ ID NO:8	10	0	18.5	4.0
	1	ND	ND	ND
SEQ ID NO:5	100	0	0	0
Raw Colostrum	100	0	0	0
	10	0	1853	1.6
	1	ND	ND	ND
	0.1	ND	ND	ND
Colostrinin	10	0	2009	17.6
	1	0	1861	7.5
	0.1	ND	ND	ND
SEQ ID NO:31	10	0	16.8	18.7
	1	0	722.9	0
	0.1	ND	ND	ND
SEQ ID NO:22	100	6.0	1630	0
	10	0	46.7	0
	1	0	0	0
	0.1	ND	ND	ND
Enfamil Low Iron	1:5	0	1913	0
Enfamil with Iron	1:5	0.4	1953	0
Control		0	0	0
SEA		16.8	866.2	0

*SEQ ID NOs:1-8 and 31, Raw Colostrum, and Colostrinin were reconstituted on the same day.
*SEQ ID NOs:18, 19, 20, and 22 were reconstituted on the same day.

Please replace the paragraph at page 30, line 1 to page 31, line 24, with the following rewritten paragraph. Per 37 C.F.R §1.121, this paragraph is also shown in Appendix A, page A, with notations to indicate the changes made.

Table 3. Relative abilities of the various peptides to induce cytokines and proliferation

	Ex. 1	Ex. 2	Ex. 1	Ex. 1	Ex. 1	Ex. 2	Ex. 1
Rank	IFN-γ	IFN-γ	Micro. Resp.	Prolif. Resp.	TNF-α	TNF-α	IL-10
1	SEQ ID NO:8	SEQ ID NO:1	SEQ ID NO:8	SEQ ID NO:2	SEQ ID NO:2**	SEQ ID NO:2	SEQ ID NO:8
2	SEQ ID NO:31	SEQ ID NO:2	SEQ ID NO:2	SEQ ID NO:1	SEQ ID NO:8	SEQ ID NO:1	SEQ ID NO:1
3	SEQ ID NO:2	SEQ ID NO:7	SEQ ID NO:31	SEQ ID NO:4	SEQ ID NO:31	SEQ ID NO:7	SEQ ID NO:3
4	SEQ ID NO:1	SEQ ID NO:22	SEQ ID NO:1	Colostrum	Colostrum	SEQ ID NO:22	SEQ ID NO:2
5	SEQ ID NO:3	SEQ ID NO:19	SEQ ID NO:7	Colostrinin	Colostrinin	SEQ ID NO:19	Colostrinin
6	Colistrinin	SEQ ID NO:20	Colostrinin	SEQ ID NO:8	SEQ ID NO:3	SEQ ID NO:20	Colostrum
7	Colustrum	SEQ ID NO:18	Colostrum	SEQ ID NO:31	SEQ ID NO:1	SEQ ID NO:18	SEQ ID NO:31
8	SEQ ID NO:4		SEQ ID NO:3	SEQ ID NO:5	SEQ ID NO:5		SEQ ID NO:4

9	SEQ ID NO:5		SEQ ID NO:4	SEQ ID NO:6	SEQ ID NO:7	Low Enfamil	SEQ ID NO:7
9	SEQ ID NO:6		SEQ ID NO:5	SEQ ID NO:7	SEQ ID NO:4	High Enfamil	SEQ ID NO:5
10	SEQ ID NO:7		SEQ ID NO:6	SEQ ID NO:3	SEQ ID NO:6		SEQ ID NO:6

* SEQ ID NO:7 < 2 fold difference in titer
** All good inducers
*** No difference in titer

Table 3. (Cont.) Relative abilities of the various peptides to induce cytokines and proliferation

Rank	Ex. 2 IL-10	Ex. 1 IL-4	Ex. 2 IL-4	Ex. 1 IL-6	Ex. 1 IL-12	Ex. 2 IL-12
1	SEQ ID NO:2	Colostrum	SEQ ID NO:1	SEQ ID NO:31	All neg.	SEQ ID NO:2
2	SEQ ID NO:7	Colostrinin	SEQ ID NO:2	SEQ ID NO:8		SEQ ID NO:1
3	SEQ ID NO:1	SEQ ID NO:31	SEQ ID NO:22	SEQ ID NO:1		
4	SEQ ID NO:19		SEQ ID NO:19	Colostrinin		
5	SEQ ID NO:22		SEQ ID NO:7	SEQ ID NO:2		

6	SEQ ID NO:20	Low Enfamil	Colostrum
7	SEQ ID NO:18		SEQ ID NO:3
8			SEQ ID NO:4
9	Low Enfamil		SEQ ID NO:6
9	High Enfamil		SEQ ID NO:5
10			SEQ ID NO:7

* SEQ ID NO:7 < 2 fold difference in titer
** All good inducers
*** No difference in titer

REMARKS

These amendments simply correct typographical errors in the documents referenced or more accurately describe the documents, and add no new matter to the specification.

The amendment to the paragraph spanning pages 8 and 9 provides the current publication number of a PCT document.

The amendment to the paragraph on page 20 corrects the publication number of a PCT document. This PCT document was correctly identified on pages 1 and 9 of the originally filed application.

The amendments to the tables on pages 26-29 and pages pages 30-31 are to correct inaccuracies in the specification. They are being corrected herein so as not to mislead the Public.

The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

CERTIFICATE UNDER 37 C.F.R. 1.8:

The undersigned hereby certifies that this paper is being deposited in the United States Postal Service, as first class mail, in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on this 11 day of June, 2001.

Ann M. Mueting

Ann M. Mueting

June 11, 2001
Date

Respectfully submitted,
Stanton et al.,
By their Representatives,
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612)305-1220
Facsimile: (612)305-1228
Customer Number 26813

By: Ann M. Mueting
Ann M. Mueting
Reg. No. 33,977
Direct Dial (612)305-1217

Appendix A
Specification Amendments with Notations to Indicate Changes Made

Applicants: Stanton et al.
Serial No.: 09/641,801 Confirmation No.: 5388
Filed: August 17, 2000

For: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

Brackets are used to signify deletions, and underlining is used to signify additions herein. The changes are also shaded in gray.

Page 8, line 32 to page 10, line 9

Colostrinin has been found to include a number of peptides ranging from 3 amino acids to 22 amino acids or more. These can be obtained by various known techniques, including isolation and purification involving eletrophoresis and synthetic techniques. The specific method of obtaining colostrinin and SEQ ID NO:31 is described in International Publication No. WO-A-98/14473. Using HPLC and Edelman Degradation, over 30 constituent peptides of colostrinin have been identified, which can be classified into several groups: (A) those of unknown precursor; (B) those having a β-casein homologue precursor; (C) those having a β-casein precursor; and (D) those having an annexin precursor. These peptides are described in International Patent [Application PCT/GB00/02128] Publication No. WO 00/75173, filed June 2, 2000, claiming priority to June 2, 1999, and can be synthesized according to the general method described in the Examples Section. These peptides (i.e., constituent peptides of colostrinin), which can be derived from colostrinin or chemically synthesized, include: MQPPPLP (SEQ ID NO:1); LQTPQPLLQVMMEPQGD (SEQ ID NO:2); DQPPDVEKPDLQPFQVQS (SEQ ID NO:3); LFFFLPVVNVLP (SEQ ID NO:4); DLEMPVLPVEPFPFV (SEQ ID NO:5); MPQNFYKLPQM (SEQ ID NO:6); VLEMKFPPPPQETVT (SEQ ID NO:7); LKPFPKLKVEVFPFP (SEQ ID NO:8); VVMEV (SEQ ID NO:9); SEQP (SEQ ID NO:10); DKE (SEQ ID NO:11); FPPPK (SEQ ID NO:12); DSQPPV (SEQ ID NO:13); DPPPPQS (SEQ ID NO:14); SEEMP (SEQ ID NO:15); KYKLQPE (SEQ ID NO:16); VLPPNVG (SEQ ID

NO:17); VYPFTGPIPN (SEQ ID NO:18); SLPQNILPL (SEQ ID NO:19); TQTPVVVPPF (SEQ ID NO:20); LQPEIMGVPKVKETMVPK (SEQ ID NO:21); HKEMPFPKYPVEPFTESQ (SEQ ID NO:22); SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23); SWMHQPP (SEQ ID NO:24); QPLPPTVMFP (SEQ ID NO:25); PQSVLS (SEQ ID NO:26); LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27); AFLLYQE (SEQ ID NO:28); RGPFPILV (SEQ ID NO:29); ATFNRYQDDHGEEILKSL (SEQ ID NO:30); VESYVPLFP (SEQ ID NO:31); FLLYQEPVLGPVR (SEQ ID NO:32); LNF (SEQ ID NO:33); and MHQPPQPLPPTVMFP (SEQ ID NO:34). These can be classified as follows: (A) those of unknown precursor include SEQ ID NOs:2, 6, 7, 8, 10, 11, 14, and 33; (B) those having a β-casein homologue precursor include SEQ ID NOs:1, 3, 4, 5, 9, 12, 13, 15, 16, 17, and 31; (C) those having a β-casein precursor include SEQ ID NOs:18 (casein amino acids 74-83), 19 (casein amino acids 84-92), 20 (casein amino acids 93-102), 21 (casein amino acids 103-120), 22 (casein amino acids 121-138), 23 (casein amino acids 139-156), 24 (casein amino acids 157-163), 25 (casein amino acids 164-173), 26 (casein amino acids 174-179), 27 (casein amino acids 180-201), 28 (casein amino acids 202-208), 29 (casein amino acids 214-222), 32 (casein amino acids 203-214), and 34 (casein amino acids 159-173); and (D) those having an annexin precursor include SEQ ID NO:30 (annexin amino acids 203-220).

Page 20, line 38 to line 41

Cytokine studies: Colostrinin has previously been shown in the literature to induce IFN-γ and TNF-α, as has Val-Glu-Ser-Tyr-Val-Pro-Leu-Phe-Pro (SEQ ID NO:31), which is disclosed in International Publication No. WO-A-[98/14447] 98/14473. Thus, studies were done to investigate the individual peptides.

Table at page 26, line 3 to page 29, line 16

Table 2. (cont.) Cytokines induced in human leukocyte cultures stimulated with CCP, colostrum or commercial milk formulas.

PEPTIDE (Exp. #)	PEPTIDE CONCENTRATION (mg/ml)	IL-4 (pg/ml)	IL-6 (pg/ml)	IL-12 (pg/ml)
Example 1				
SEQ ID NO:1	100	0	235.4	0
	10	0	934.8	0
	1	0	675.3	0
	0.1	0	497.1	0
SEQ ID NO:7	100	0	291.3	0
	10	0	645.4	0
SEQ ID NO:8	100	0	1076	0
	10	0	1024	0
	1	0	1013	0
	0.1	0	533.6	0
SEQ ID NO:3	1	0	620.5	0
	0.1	0	107	0
SEQ ID NO:2	100	0	258.6	0
	10	0	551.3	0
	1	0	1205	0
	0.1	0	325	0
SEQ ID NO:4	10	0	1718	0
	1	0	744.4	0

SEQ ID NO:5	100	0	98.2	0
	10	0	750	0
SEQ ID NO:6	100	0	63.3	0
	10	0	864.5	0
SEQ ID NO:31	100	1.4	1489	0
	10	0	836.3	0
	1	0.4	489.9	0
	0.1	2.4	1635	0
Colostrinin	10	0	1832	0
	1	1.9	1915	0
	0.1	0.4	430.1	0
Raw Colostrum	100	0	1879	0
	10	0	602.2	0
	1	0	1055	0
	0.1	5.0	187.2	0
Control		0	13.5	0
SEA		4	1704	0

Example 2

SEQ ID NO:18	100	0	[142.4]	
0				
SEQ ID NO:19	10	0	[549.7]	0
	1	33.8	[1552]	0
SEQ ID NO:20	100	0	[50]	0
	10	0.4	[105.9]	0

SEQ ID NO:22	100	41.5	[808.6]	0
	10	32.7	[503.2]	0
	1	30.1	[1005]	0
	0.1	17.8	[396.4]	0
SEQ ID NO:1	100	0	[1471]	0
	10	3.5	[96.5]	5.7
	1	26.6	[626.6]	0
	0.1	47.6	[1385]	0
SEQ ID NO:7	100	24.5	[1546]	0
SEQ ID NO:2	100	22.5	[1292]	33.5
	10	19.9	[1516]	0
	1	10.1	[1886]	9.9
	0.1	29.1	[478.3]	2.2
Enfamil Low Iron	1:5	0.9	[1757]	0
	1:10	4.0	[1958]	0
Enfamil with Iron	1:5	0	[1909]	0
	1:10	0	[ND]	0
Control		0	[183.5]	0
SEA		62.5	[1769]	54.8
Example 3				
SEQ ID NO:1	100	0	942.5	0
	10	ND	ND	ND
SEQ ID NO:7	1	0	32.9	0
	0.1	ND	ND	ND
SEQ ID NO:8	10	0	18.5	4.0
	1	ND	ND	ND

SEQ ID NO:5	100	0	0	0
Raw	100	0	0	0
Colostrum	10	0	1853	1.6
	1	ND	ND	ND
	0.1	ND	ND	ND
Colostrinin	10	0	2009	17.6
	1	0	1861	7.5
	0.1	ND	ND	ND
SEQ ID NO:31	10	0	16.8	18.7
	1	0	722.9	0
	0.1	ND	ND	ND
SEQ ID NO:22	100	6.0	1630	0
	10	0	46.7	0
	1	0	0	0
	0.1	ND	ND	ND
Enfamil Low Iron	1:5	0	1913	0
Enfamil with Iron	1:5	0.4	1953	0
Control		0	0	0
SEA		16.8	866.2	0

*SEQ ID NOs:1-8 and 31, Raw Colostrum, and Colostrinin were reconstituted on the same day.
*SEQ ID NOs:18, 19, 20, and 22 were reconstituted on the same day.

Table at page 30, line 1 to page 31, line 24

Table 3. Relative abilities of the various peptides to induce cytokines and proliferation

	Ex. 1	Ex. 2	Ex. 1	Ex. 1	Ex. 1	Ex. 2	Ex. 1
Rank	IFN-γ	IFN-γ	Micro. Resp.	Prolif. Resp.	TNF-α	TNF-α	IL-10
1	SEQ ID NO:8	SEQ ID NO:1	SEQ ID NO:8	SEQ ID NO:2	SEQ ID NO:2**	SEQ ID NO:2	SEQ ID NO:8
2	SEQ ID NO:31	SEQ ID NO:2	SEQ ID NO:2	SEQ ID NO:1	SEQ ID NO:8	SEQ ID NO:1	SEQ ID NO:1
3	SEQ ID NO:2	SEQ ID NO:7	SEQ ID NO:31	SEQ ID NO:4	SEQ ID NO:31	SEQ ID NO:7	SEQ ID NO:3
4	SEQ ID NO:1	SEQ ID NO:22	SEQ ID NO:1	Colostrum	Colostrum	SEQ ID NO:22	SEQ ID NO:2
5	SEQ ID NO:3	SEQ ID NO:19	SEQ ID NO:7	Colostrinin	Colostrinin	SEQ ID NO:19	Colostrinin
6	Colistrinin	SEQ ID NO:20	Colostrinin	SEQ ID NO:8	SEQ ID NO:3	SEQ ID NO:20	Colostrum
7	Colustrum	SEQ ID NO:18	Colostrum	SEQ ID NO:31	SEQ ID NO:1	SEQ ID NO:18	SEQ ID NO:31
8	SEQ ID NO:4		SEQ ID NO:3	SEQ ID NO:5	SEQ ID NO:5		SEQ ID NO:4
9	SEQ ID NO:5		SEQ ID NO:4	SEQ ID NO:6	SEQ ID NO:7	Low Enfamil	SEQ ID NO:7
9	SEQ ID NO:6		SEQ ID NO:5	SEQ ID NO:7	SEQ ID NO:4	High Enfamil	SEQ ID NO:5

10	SEQ ID NO:7	SEQ ID NO:6	SEQ ID NO:3	SEQ ID NO:6		SEQ ID NO:6

* SEQ ID NO:7 < 2 fold difference in titer
** All good inducers
*** No difference in titer

Table 3. (Cont.) Relative abilities of the various peptides to induce cytokines and proliferation

Rank	Ex. 2 IL-10	Ex. 1 IL-4	Ex. 2 IL-4	Ex. 1 IL-6	[Ex. 2] [IL-6]	Ex. 1 IL-12	Ex. 2 IL-12
1	SEQ ID NO:2	Colostrum	SEQ ID NO:1	SEQ ID NO:31	[Control]	All neg.	SEQ ID NO:2
2	SEQ ID NO:7	Colostrinin	SEQ ID NO:2	SEQ ID NO:8			SEQ ID NO:1
3	SEQ ID NO:1	SEQ ID NO:31	SEQ ID NO:22	SEQ ID NO:1			
4	SEQ ID NO:19		SEQ ID NO:19	Colostrinin			
5	SEQ ID NO:22		SEQ ID NO:7	SEQ ID NO:2			
6	SEQ ID NO:20		Low Enfamil	Colostrum			
7	SEQ ID NO:18			SEQ ID NO:3			
8				SEQ ID NO:4			

9	Low Enfamil	SEQ ID NO:6
9	High Enfamil	SEQ ID NO:5
10		SEQ ID NO:7

* SEQ ID NO:7 < 2 fold difference in titer
** All good inducers
*** No difference in titer

Receipt is hereby acknowledged for the following in the U.S. Patent and Trademark Office:

Applicant(s): Stanton et al.
Serial No.: 09/641,801
Filed: August 17, 2000
Title: USES OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

Enclosed: Amendment and Response including Appendix A and Exhibit A (36 pgs).; An Information Disclosure Statement (2 pgs), 1449 form (1 pg); and copies of 4 documents cited on the 1449 forms; Check in the amount of $180.00, representing Information Disclosure Statement Fee; and transmittal document (in triplicate).

Mailed: December 4, 2002
Docket: 265.00230101

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Stanton et al.	Group Art Unit:	1647
Serial No.:	09/641,801	Examiner:	C. Nichols
Confirmation No.:	5388		
Filed:	August 17, 2000		

For: USES OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

AMENDMENT AND RESPONSE

Assistant Commissioner for Patents
Washington D.C. 20231

Dear Sir:

In response to the Office Action mailed September 4, 2002, please amend the above-identified application as follows:

In the Specification

Please replace the paragraph beginning at page 6, line 32, with the following rewritten paragraph. Per 37 C.F.R. §1.121, this paragraph is also shown in Appendix A with notations to indicate the changes made.

Many nonspecific and specific immune responses are associated with leukocyte proliferation and differentiation. The overall immunological significance of the present invention can be, but is not limited to, the following: IFN-γ is a potent immunomodulater that is important for the development of the cytotoxic lymphocyte response (CTL). This immune response is considered to be very important in protecting humans and animals from a variety of bacterial, viral, parasitic, and fungal diseases. The fact that TNF-α is also induced is important because TNF-α is a major activator of macrophages, among other immune cells, which are important in

host defense against infections. In addition, TNF-α has been shown to have activity against cancer, directly through its lytic activity and indirectly through macrophages. IL-10 is another important immune mediator that controls both IFN-γ and TNF-α production and action. Its production represent a negative feedback control for IFN-γ and TNF-α production. Another one of its hallmark activities is the control of antibody production during the humoral immune responses, which is certainly important in many types of infections. In addition to IL-10's immune activities, it also has been shown to play a role in the neuroendocrine system by modulating certain stress responses and immune responses. IL-10 has been shown to induce the production of corticotropin from pitutitary cells. Corticotropin works downstream in the hypothalmic adrenal axis to induce glucocortico steroids that are inherently immunomodulatory. Like IL-10, the IL-4 is important in the development of B cell responses, which are the mediators of the humoral immune response. Finally, the IL-12 is an important IFN-γ inducer. Taken together these findings suggest that colostrinin and its component peptides have the ability to modulate via cytokine induction a variety of host-defense mechanisms mediated by macrophages and lymphocytes at the cellular and humoral immune level as well as the neuroendocrine system.

Please replace the paragraph beginning at page 11, line 29, with the following rewritten paragraph. Per 37 C.F.R. §1.121, this paragraph is also shown in Appendix A with notations to indicate the changes made.

As stated above, active analogs of colostrinin and its constituent peptides include polypeptides having structural similarity. Structural similarity is generally determined by aligning the residues of the two amino acid sequences to optimize the number of identical amino acids along the lengths of their sequences; gaps in either or both sequences are permitted in making the alignment in order to optimize the number of identical amino acids, although the amino acids in each sequence must nonetheless remain in their proper order. Preferably, two

amino acid sequences are compared using the Blastp program, version 2.0.9, of the BLAST 2 search algorithm, available on the worldwide web at ncbi.nlm.nih.gov/gorf/b12.html. Preferably, the default values for all BLAST 2 search parameters are used, including matrix = BLOSUM62; open gap penalty = 11, extension gap penalty = 1, gap x_dropoff = 50, expect = 10, wordsize = 3, and filter on. In the comparison of two amino acid sequences using the BLAST search algorithm, structural similarity is referred to as "identity." Preferably, an active analog of colostrinin or its constituent peptides has a structural similarity to colostrinin or one or more of its constituent peptides (preferably, one of SEQ ID NOs:1-30) of at least about 70% identity, more preferably, at least about 80% identity, and most preferably, at least about 90% identity.

In the Claims

Please cancel claims 5, 10, 12 and 36, amend claims 1, 6, 11, 20-29 and 31-35, and add new claims 37-39. The new and amended claims are provided below in clean form. Per 37 C.F.R. §1.121, amended claims are also shown in Appendix A with notations to indicate changes made (for convenience, all pending claims, including those added hereby, are provided in Appendix A).

1. [AMENDED] A method of inducing a cytokine in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator comprises MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1.

6. [AMENDED] A method for modulating an immune response in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator comprises MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1.

11. [AMENDED] A method for modulating an immune response in a patient, the method comprising administering to the patient an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator comprises MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1.

20. [AMENDED] A method for modulating leukocyte proliferation, the method comprising contacting leukocytes with a leukocyte regulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, under conditions effective to change the number of leukocyte; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

21. [AMENDED] The method of claim 20 wherein the leukocytes are present in a cell culture or an organism.

22. [AMENDED] The method of claim 20 wherein the leukocytes are mammalian cells.

23. [AMENDED] The method of claim 22 wherein the leukocytes are human cells.

24. [AMENDED] The method of claim 22 wherein the leukocytes are increased in number.

25. [AMENDED] The method of claim 24 wherein the leukocytes are differentiated.

26. [AMENDED] The method of claim 22 wherein the leukocyte regulator is a constituent peptide of colostrinin.

27. [AMENDED] The method of claim 26 wherein the leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more

constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

28. [AMENDED] The method of claim 27 wherein the leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8), YPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

29. [AMENDED] A method for modulating leukocyte proliferation in a patient, the method comprising administering to the patient a leukocyte regulator selected from the group of colostrinin, a constituent peptide thereof, an analog thereof, and combinations thereof, under conditions effective to change the number of leukocytes; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

31. [AMENDED] The method of claim 29 wherein the leukocytes are increased in number.

32. [AMENDED] The method of claim 31 wherein the leukocytes are differentiated.

33. [AMENDED] The method of claim 29 wherein the leukocyte regulator is a constituent peptide of colostrinin.

34. [AMENDED] The method of claim 33 wherein the leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

35. [AMENDED] The method of claim 34 wherein the leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8),VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

37. [NEW] A method of inducing a cytokine in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more a constituent peptides of colostrinin which are selected from the group of SEQ ID NO:2-30 and 32-34.

38. [NEW] A method for modulating an immune response in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4),

DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin which are selected from the group of SEQ ID NO:2-30 and 32-34.

39. [NEW] A method for modulating an immune response in a patient, the method comprising administering to the patient an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID

NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin which are selected from the group of SEQ ID NO:2-30 and 32-34.

Remarks

The Office Action mailed September 4, 2002 has been received and reviewed. Claims 1, 6, 11, 20-29 and 31-35 having been amended, claims 5, 10, 12, and 36 having been canceled and claims 37-39 having been added, the pending claims are claims 1-4, 6-9, 11, 13-35 and 37-39. Reconsideration and withdrawal of the rejections are respectfully requested.

The claims have been amended to clarify the claimed invention. Claim amendments have not been made to narrow the claimed invention. Support for claims amendments is found throughout the specification. For example, support for the amendment "wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1" in claims 1, 6, 11, 20, 27, 29 and 34 is found on p. 11, line 24 and p. 12, lines 11-13 of the specification. Support for the amendment "leukocyte" in claims 20-29 and 31-35 is found on p.2, line 17 of the specification. Support for new claim 37 is found in original claim 1; support for new claim 38 is found in original claim 6; and support for new claim 39 is found in original claim 11.

Traverse of Restriction Requirement

In response to the Restriction Requirement mailed June 17, 2002, Applicants elected, with traverse, Group 1 (claims 1-35), drawn to methods of contacting cells with SEQ ID NO:1 (Response to Restriction Requirement, filed July 17, 2002). Applicants continue to traverse this Restriction Requirement. Applicants submit that the restriction requirement, limiting Applicant to only one of SEQ ID NO:1-35, places an undue burden on the Applicants by requiring payment of 34 separate filing fees for examination of the nonelected claims, as well as the added costs associated with prosecuting 35 applications and maintaining 35 patents.

Further, Applicants direct the Examiner's attention to the fact that claims 20 and 29 are linking claims with respect to the use of the sequences in a method for modulating leukocyte proliferation. Accordingly, the Examiner's restriction appears to be more

appropriately an election of species with respect to specific sequences. See MPEP 809.02. Thus, Applicants traverse on the grounds that the generic (linking) claims 20 and 29 includes sufficiently few species that a search and examination of all the species at one time would not impose a serious burden on the Examiner. Applicants also request rejoinder and that the requirement be withdrawn upon the finding of an allowable genus.

Examiner Interview

An Examiner's Interview was held on October 15, 2002 between the Applicant's Representative and Examiners Nichols and Kemmerer. The claim rejections of record were discussed. Examiner Nichols and Kemmerer are thanked for the courtesy of this interview.

Information Disclosure Statements

Copies of PTO-1449s mailed June 11, 2001, and July 23, 2001, were considered by the Examiner on August 19, 2002, and included with the office action. It is noted that only some of the citations listed on the PTO-1449 mailed June 11, 2001, were considered and initialed by the Examiner. The Examiner is requested to provide an explanation of why citations on the PTO-1449 mailed on June 11, 2001 were not considered and initialed by the Examiner. As a courtesy, a copy of the PTO-1449 mailed June 11, 2001 is included as Exhibit A with this communication, for consideration by the Examiner.

Objections to the Specification

The Examiner objected to the specification for the following informalities; the misspelling of "downstream" on p.7, line19, and the recitation of a browser-executable hyperlink on p. 12, line 6. The specification has been amended to correct this spelling error and to remove the browser-executable hyperlink. Withdrawal of the objection to the specification is respectfully requested.

Objections to the Claims

The Examiner has objected to claims 1-35 for the recitation of non-elected inventions. Claims 1-4, 6-9, 11, 13-19, 27 and 34 have been amended to recite elected SEQ ID NO:1. Claims 20-26 and 29-33, as generic claims, need not be restricted to the elected SEQ ID NO:1. Withdrawal of this objection to the claims is respectfully requested.

The 35 U.S.C. §112, First Paragraph, Rejection

The Examiner rejected claims 1-35 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is respectfully traversed.

Specifically, the Examiner stated that the specification does not enable one of skill in the art to practice the claimed invention with all "analogs." Claims 1-4, 6-9, 11, 13-19, 27, 28 and 34 are drawn to active analogs of SEQ ID NO:1, "wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1." It is respectfully submitted that the specification provides ample guidance to allow one of skill in the art to make and use active analogs having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1. See, for example, p. 11, line 21 through p. 12, line 15 of the specification.

Further, the Examiner stated that the specification does not enable one of skill in the art to practice the claimed invention to modulate "the enormous range of blood cells." Claims 20-35 are drawn to leukocytes. Leukocytes, the white blood cell component of blood, are much less numerous than red blood cell component of blood, (the ratio between the two is around 1:700). It is respectfully submitted that the specification provides ample guidance to practice the claimed methods of modulating leukocyte proliferation. See, for example, Table 1, pages 19-20 of the specification, demonstrating the proliferation of human leukocyte cultures.

Withdrawal of this rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

The 35 U.S.C. §102 Rejection over Inglot et al.

The Examiner rejected claims 1-10 under 35 U.S.C. §102 as being anticipated by Inglot et al. (1996) Archivum Immunologiae et Therapiae Experimentalis 44:215-224. This rejection is respectfully traversed. It is respectfully submitted that Inglot et al. does not disclose methods of inducing a cytokine in a cell (claims 1-4) or modulating an immune response in a cell (claims 6-9) comprising contacting the cell with a peptide comprising SEQ ID NO:1, an active analog thereof, and combinations thereof, wherein an "active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1." Thus, the disclosure of Inglot et al. does not set forth each and every element of claims 1-10. According to MPEP § 2131 a "claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Withdrawal of this rejection under 35 U.S.C. §102(a) is respectfully requested.

The 35 U.S.C. §102 Rejection over Janusz et al.

The Examiner rejected claims 11-35 under 35 U.S.C. §102 as being anticipated by Janusz et al. (WO 98/14473). This rejection is respectfully traversed.

It is respectfully submitted that Janusz et al. does not disclose a method of modulating an immune response (claims 11, 13-19) or a method of modulating leukocyte proliferation (claims 27, 28, 34 and 35) comprising the administration of SEQ ID NO:1, an active analog thereof, and combinations thereof, wherein an "active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1." Thus, the disclosure of Janusz et al. does not

set forth each and every element of the claimed invention and withdrawal of this rejection under 35 U.S.C. §102(a), as anticipated by Janusz et al., is respectfully requested.

Further, it is respectfully submitted that Janusz et al. does not disclose a method of modulating leukocyte proliferation (claims 20-35), where proliferation is an increase in cell number (see p. 8, lines 10-15 and p. 18, lines 1-32 of the specification). Rather, the teachings of Janusz et al. are limited to the administration of colostrinin to provide an "immunotrophic action" (p. 1, line 30); to improve "the development of the immune system" (p.3, lines 15-16); "to stimulate the growth, maturation and differentiation of immunologically active cells" (p. 8, lines 4-5); and to stimulate the production of cytokines (p. 8., lines 7-10). Janusz et al. does not disclose an increase in leukocyte cell numbers, thus Janusz et al. does not disclose modulation of the proliferation of leukocytes.

The Examiner uses the doctrine of inherency to support these rejections. However, Applicants' Representatives submit that historically the inherency doctrine has been used to reject claims to a product that is alleged to be new when there is a process in the prior art that clearly yields the claimed product. The Examiner is requested to note that all the currently pending claims are directed to methods.

Furthermore, for inherency to apply, the missing descriptive information must necessarily be present in one of the cited documents such that one of skill in the art would recognize such a disclosure. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill'" (In re Robertson, 49 USPQ2d 1949 (Fed. Cir. 1999) quoting Continental Can Co. v. Monsanto Co., 20 USPQ2d 1746 (Fed. Cir. 1991)).

Because the claimed methods are drawn to methods of modulating leukocyte proliferation comprising the administration of a leukocyte regulator "under conditions effective to change the number of leukocytes" (claims 20-35), there can be no recognition by one of skill in the art that modulating leukocyte proliferation is necessarily present in the teachings of Janusz

et al. Inherency must be a necessary result, not merely a possible result. "'Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" (In re Robertson, 49 USPQ2d 1949 (Fed. Cir. 1999) quoting In re Oelrich, 212 USPQ 323 (Fed. Cir. 1981)). Furthermore, methods of modulating leukocyte proliferation are inherent only if there is at least a reasonable likelihood that one of skill in the art could have discovered or recognized it without specific guidance. That is, the subject matter relied upon must be disclosed in a manner to place it in possession of the public. (See, e.g., Akzo N.V. v. United States Int'l Trade Comm'n, 1 USPQ2d 1241 (Fed. Cir. 1986)). Clearly, this is not the situation with the documents cited by the Examiner. The teachings of Janusz et al. are limited to immunotrophic events, such as inflammation, and include no recognition of leukocyte proliferation.

For the reasons discussed above, the disclosure of Janusz et al. does not set forth each and every element of the invention of claims 10-35. Withdrawal of this rejection under 35 U.S.C. §102(a) is respectfully requested.

Summary

It is respectfully submitted that the pending claims 1-4, 6-9, 11, 13-35 and 37-39 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
Stanton et al.

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

26813

PATENT TRADEMARK OFFICE

December 4, 2002
Date

By: _____

Loren D. Albin
Reg. No. 37,763
Direct Dial (612)305-1217

CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: EV 183606717 US Date of Deposit: December 4, 2002
The undersigned hereby certifies that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

By: _____
Name: Sara E. Olson

APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS INCLUDING NOTATIONS TO INDICATE CHANGES MADE
Serial No.: 09/641,801
Docket No.: 265.00230101

Amendments to the following are indicated by underlining what has been added and bracketing what has been deleted.

In the Specification

The paragraph beginning at page 6, line 32, has been amended as follows:

Many nonspecific and specific immune responses are associated with leukocyte proliferation and differentiation. The overall immunological significance of the present invention can be, but is not limited to, the following: IFN-γ is a potent immunomodulater that is important for the development of the cytotoxic lymphocyte response (CTL). This immune response is considered to be very important in protecting humans and animals from a variety of bacterial, viral, parasitic, and fungal diseases. The fact that TNF-α is also induced is important because TNF-α is a major activator of macrophages, among other immune cells, which are important in host defense against infections. In addition, TNF-α has been shown to have activity against cancer, directly through its lytic activity and indirectly through macrophages. IL-10 is another important immune mediator that controls both IFN-γ and TNF-α production and action. Its production represent a negative feedback control for IFN-γ and TNF-α production. Another one of its hallmark activities is the control of antibody production during the humoral immune responses, which is certainly important in many types of infections. In addition to IL-10's immune activities, it also has been shown to play a role in the neuroendocrine system by modulating certain stress responses and immune responses. IL-10 has been shown to induce the production of corticotropin from pitutitary cells. Corticotropin works <u>downstream</u> [downstreanm] in the hypothalmic adrenal axis to induce glucocortico steroids that are inherently immunomodulatory. Like IL-10, the IL-4 is important in the development of B cell responses, which are the mediators of the humoral immune response. Finally, the IL-12 is an important IFN-γ inducer. Taken together these findings suggest that colostrinin and its component peptides have the ability to modulate via cytokine induction a variety of host-defense

mechanisms mediated by macrophages and lymphocytes at the cellular and humoral immune level as well as the neuroendocrine system.

The paragraph beginning at page 11, line 29, has been amended as follows:

As stated above, active analogs of colostrinin and its constituent peptides include polypeptides having structural similarity. Structural similarity is generally determined by aligning the residues of the two amino acid sequences to optimize the number of identical amino acids along the lengths of their sequences; gaps in either or both sequences are permitted in making the alignment in order to optimize the number of identical amino acids, although the amino acids in each sequence must nonetheless remain in their proper order. Preferably, two amino acid sequences are compared using the Blastp program, version 2.0.9, of the BLAST 2 search algorithm, available on the worldwide web at ncbi.nlm.nih.gov/gorf/b12.html [at http://www.ncbi.nlm.nih.gov/gorf/bl2.html]. Preferably, the default values for all BLAST 2 search parameters are used, including matrix = BLOSUM62; open gap penalty = 11, extension gap penalty = 1, gap x_dropoff = 50, expect = 10, wordsize = 3, and filter on. In the comparison of two amino acid sequences using the BLAST search algorithm, structural similarity is referred to as "identity." Preferably, an active analog of colostrinin or its constituent peptides has a structural similarity to colostrinin or one or more of its constituent peptides (preferably, one of SEQ ID NOs:1-30) of at least about 70% identity, more preferably, at least about 80% identity, and most preferably, at least about 90% identity.

In the Claims

For convenience, all pending claims are shown below.

1. [AMENDED] A method of inducing a cytokine in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator comprises [is selected from the group of]

MQPPPLP (SEQ ID NO:1), [LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34),] an active analog thereof, and combinations thereof, [with the proviso that the immunological regulator is not VESYVPLFP (SEQ ID NO:31)] wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1.

2. The method of claim 1 wherein the cell is present in a cell culture, a tissue, an organ, or an organism.

3. The method of claim 1 wherein the cell is a mammalian cell.

4. The method of claim 3 wherein the cell is a human cell.

5. [CANCEL] The method of claim 1 wherein the immunological regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2),

DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8),VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

6. [AMENDED] A method for modulating an immune response in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator comprises [is selected from the group of] MQPPPLP (SEQ ID NO:1), [LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34),] an active analog thereof, and combinations thereof, [with the proviso that the immunological regulator is not VESYVPLFP (SEQ ID NO:31)] wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1.

7. The method of claim 6 wherein the cell is present in a cell culture, a tissue, an organ, or an organism.

8. The method of claim 6 wherein the cell is a mammalian cell.

9. The method of claim 8 wherein the cell is a human cell.

10. [CANCEL] The method of claim 6 wherein the immunological regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

11. [AMENDED] A method for modulating an immune response in a patient, the method comprising administering to the patient an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator <u>comprises</u> [is selected from the group of] MQPPPLP (SEQ ID NO:1), [LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID

NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34),] an active analog thereof, and combinations thereof, [with the proviso that the immunological regulator is not VESYVPLFP (SEQ ID NO:31)] wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1.

12. [CANCEL] The method of claim 11 wherein the immunological regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

13. The method of claim 11 wherein the immunological regulator is administered as part of a dietary supplement.

14. The method of claim 11 wherein the immunological regulator is administered topically.

15. The method of claim 11 wherein the patient is an animal.

16. The method of claim 15 wherein the patient is a human.

17. The method of claim 11 wherein the immune response is a specific immune response.

18. The method of claim 11 wherein the immune response is a nonspecific immune response.

19. The method of claim 11 wherein the immune response is the interferon response or antibody production.

20. [AMENDED] A method for modulating [blood cell] leukocyte proliferation, the method comprising contacting [blood cells] leukocytes with a [blood cell] leukocyte regulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, under conditions effective to change the number of [blood cell] leukocyte; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

21. [AMENDED] The method of claim 20 wherein the [blood cells] leukocytes are present in a cell culture or an organism.

22. [AMENDED] The method of claim 20 wherein the [blood cells] leukocytes are mammalian cells.

23. [AMENDED] The method of claim 22 wherein the [blood cells] leukocytes are human cells.

24. [AMENDED] The method of claim 22 wherein the [blood cells] leukocytes are increased in number.

25. [AMENDED] The method of claim 24 wherein the [blood cells] leukocytes are differentiated.

26. [AMENDED] The method of claim 22 wherein the [blood cell] leukocyte regulator is a constituent peptide of colostrinin.

27. [AMENDED] The method of claim 26 wherein the [blood cell] leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

28. [AMENDED] The method of claim 27 wherein the [blood cell] leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8), YPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

29. [AMENDED] A method for modulating [blood cell] leukocyte proliferation in a patient, the method comprising administering to the patient a [blood cell] leukocyte regulator selected from the group of colostrinin, a constituent peptide thereof, an analog thereof, and combinations thereof, under conditions effective to change the number of [blood cells] leukocytes; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

30. The method of claim 29 wherein the patient is a human.

31. [AMENDED] The method of claim 29 wherein the [blood cells] leukocytes are increased in number.

32. [AMENDED] The method of claim 31 wherein the [blood cells] leukocytes are differentiated.

33. [AMENDED] The method of claim 29 wherein the [blood cell] leukocyte regulator is a constituent peptide of colostrinin.

34. [AMENDED] The method of claim 33 wherein the [blood cell] leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

35. [AMENDED] The method of claim 34 wherein the [blood cell] leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8),VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

36. [CANCEL] A cytokine-inducing composition comprising a pharmaceutical carrier and an active agent selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, with the proviso that the active agent is not VESYVPLFP (SEQ ID NO:31).

37. [NEW] A method of inducing a cytokine in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ

ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to a one or more constituent peptides of colostrinin which are selected from the group of SEQ ID NO:2-30 and 32-34.

38. [NEW] A method for modulating an immune response in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP

(SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin which are selected from the group of SEQ ID NO:2-30 and 32-34.

39. [NEW] A method for modulating an immune response in a patient, the method comprising administering to the patient an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin which are selected from the group of SEQ ID NO:2-30 and 32-34.

INFORMATION DISCLOSURE STATEMENT	Atty. Docket No.: 265.0023 0101	Serial No.: 09/641,801
	Applicant(s): Stanton et al.	Confirmation No.: 5388
	Filing Date: August 17, 2000	Group: 1653

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
		4,938,949	07/03/90	Borch et al.			
		5,595,887	01/21/97	Coolidge et al.			

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation	
							Yes	No
		WO 98/14473	04/09/98	PCT				
		WO 99/65329	12/23/99	PCT				
		WO 00/75173	12/14/00	PCT				
		WO 01/11937	02/22/01	PCT				
		WO 01/12650	02/22/01	PCT				
		WO 01/12651	02/22/01	PCT				

OTHER DOCUMENTS (Including Authors, Title, Date, Pertinent Papers, etc.)

			Babbit, ed., *The Vanderbilt Rubber Handbook*, R.T. Vanderbilt Company, Inc., Norwalk, CT, pp. 344-397 (1978).
			Bespalov et al., "Fabs specific for 8-oxoguanine: control of DNA binding," *J Mol Biol.* 1999 Nov 12;*293*(5):1085-95.
			Blach-Olszewska et al., "Stimulatory effect of ovine colostrinine (a proline-rich polypeptide) on interferons and tumor necrosis factor production by murine resident peritoneal cells," *Arch Immunol Ther Exp (Warsz).* 1997;*45*(1):43-7.
			"BLAST," National Institutes of Health [online] Bethesda, M.D. Retrieved from the Internet on May 14, 2001:<URL:http://www.ncbi.nlm.nih.gov/gorf/bl2.html>, 1 pg.
			Buescher et al., "Colostral antioxidants: separation and characterization of two activities in human colostrum," *J Pediatr Gastroenterol Nutr*1. 1992 Jan; *14*(1):47-56.
			Calingasan et al., "Protein-bound acrolein: a novel marker of oxidative stress in Alzheimer's disease," *J Neurochem.* 1999 Feb;*72*(2):751-6.

EXAMINER	Date Considered

*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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			Chao "Growth factor signaling: where is the specificity?" *Cell.* 1992 Mar 20;*68*(6):995-7.
			Esterbauer et al., "Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes," *Free Radic Biol Med.* 1991;*11*(1):81-128.
			Fields et al., *Synthetic Peptides: A User's Guide*, W.M. Freeman & Company, New York, NY, pp. 77-183 (1992).
			Fillmore et al., "Differentiation of PC12 cells with nerve growth factor is associated with induction of transin synthesis and release," *J Neurosci Res.* 1992 Apr;*31*(4):662-9.
			Gabbita et al., "Increased nuclear DNA oxidation in the brain in Alzheimer's disease," *J Neurochem.* 1998 Nov;*71*(5):2034-40.
			Gabbita et al., "Decrease in peptide methionine sulfoxide reductase in Alzheimer's disease brain," *J Neurochem.* 1999 Oct;*73*(4):1660-6.
			Good et al., "Evidence of neuronal oxidative damage in Alzheimer's disease," *Am J Pathol.* 1996 Jul;*149*(1):21-8.
			Gratama et al., "Flow cytometric quantitation of immunofluorescence intensity: problems and perspectives. European Working Group on Clinical Cell Analysis," *Cytometry.* 1998 Oct 1;*33*(2):166-78.
			Grunwald et al., "In situ analysis of chromatin proteins during development and cell differentiation using flow cytometry," *Methods Mol Biol.* 1999;*119*:443-54.
			Hensley et al., "Brain regional correspondence between Alzheimer's disease histopathology and biomarkers of protein oxidation," *J Neurochem.* 1995 Nov; *65*(5):2146-56.
			Hughes et al., "Modulation of immune responses by anabolic androgenic steroids," *Int J Immunopharmacol.* 1995 Nov;*17*(11):857-63.
			Inglot et al., "Colostrinine: a proline-rich polypeptide from ovine colostrum is a modest cytokine inducer in human leukocytes," *Arch Immunol Ther Exp (Warsz).* 1996;*44*(4):215-24.
			Inglot et al., "Colostrinin for treatment of Alzheimer's disease," *European Cytokine Network.* 1996 Sept;7(3):458(abstract 51).

EXAMINER	Date Considered

*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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	Applicant(s): Stanton et al.	Confirmation No.: 5388
	Filing Date: August 17, 2000	Group: 1653

			Inglot et al., "Tumor-associated antigens are cytokine inducers and hyporeactivity factors to the immune system," *Biotherapy*. 1998;*11*(1):27-37.
			Janusz et al., "Isolation and characterization of a proline-rich polypeptide from ovine colostrum," *FEBS Lett*. 1974 Dec 15;*49*(2):276-9.
			Janusz et al., "Chemical and physical characterization of a proline-rich polypeptide from sheep colostrum," *Biochem J*. 1981 Oct 1;*199*(1):9-15.
			Janusz et al., "Proline-rich polypeptide (PRP) - an immunomodulatory peptide from ovine colostrum," *Arch Immunol Ther Exp (Warsz)*. 1993;*41*(5-6):275-9.
			Kim et al., "Simultaneous differentiation and quantitation of erythroblasts and white blood cells on a high throughput clinical haematology analyser," *Clin Lab Haematol*. 1998 Feb;*20*(1):21-9.
			Kooy et al., "Oxidation of 2',7'-dichlorofluorescin by peroxynitrite," *Free Radic Res*. 1997 Sep;*27*(3):245-54.
			LeBel et al., "Evaluation of the probe 2',7'-dichlorofluorescin as an indicator of reactive oxygen species formation and oxidative stress," *Chem Res Toxicol*. 1992 Mar-Apr;*5*(2):227-31.
			Leszek et al., "Colostrinin: a proline-rich polypeptide (PRP) complex isolated from ovine colostrum for treatment of Alzheimer's disease. A double-blind, placebo-controlled study," *Arch Immunol Ther Exp (Warsz)*. 1999;*47*(6):377-85.
			Levi et al., "The mode of action of nerve growth factor in PC12 cells," *Mol Neurobiol*. 1988 Fall;*2*(3):201-26.
			Lovell et al., "Elevated thiobarbituric acid-reactive substances and antioxidant enzyme activity in the brain in Alzheimer's disease," *Neurology*. 1995 Aug; *45*(8):1594-601.
			Lovell et al., "Elevated 4-hydroxynonenal in ventricular fluid in Alzheimer's disease," *Neurobiol Aging*. 1997 Sep-Oct;*18*(5):457-61.
			Lovell et al., "Decreased glutathione transferase activity in brain and ventricular fluid in Alzheimer's disease," *Neurology*. 1998 Dec;*51*(6):1562-6.
			Lovell et al., "Increased DNA oxidation and decreased levels of repair products in Alzheimer's disease ventricular CSF," *J Neurochem*. 1999 Feb;*72*(2):771-6.

EXAMINER	Date Considered

*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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	Applicant(s): Stanton et al.	Confirmation No.: 5388
	Filing Date: August 17, 2000	Group: 1653

			Lovell et al., "Decreased base excision repair and increased helicase activity in Alzheimer's disease brain," *Brain Res.* 2000 Feb 7;*855*(1):116-23.
			Markesberry, "Oxidative stress hypothesis in Alzheimer's disease," *Free Radic Biol Med.* 1997;*23*(1):134-47.
			Markesbery et al., "Four-hydroxynonenal, a product of lipid peroxidation, is increased in the brain in Alzheimer's disease," *Neurobiol Aging.* 1998 Jan-Feb;*19*(1):33-6.
			Markesbery et al. "Oxidative alterations in Alzheimer's disease," *Brain Pathol.* 1999 Jan;*9*(1):133-46.
			Marshall et al., "Specificity of receptor tyrosine kinase signaling: transient versus sustained extracellular signal-regulated kinase activation," *Cell.* 1995 Jan *27*;80(2):179-85.
			McHeyzer-Williams et al., "Enumeration and characterization of memory cells in the TH compartment," *Immunol Rev.* 1996 Apr;*150*:5-21.
			Mecocci et al., "Oxidative damage to mitochondrial DNA is increased in Alzheimer's disease," *Ann Neurol.* 1994 Nov;*36*(5):747-51.
			Mishell et al., *Selected Methods in Cellular Immunology*, W.H. Freeman, San Francisco, CA; title page and table of contents only, 9 pages (1980).
			Montine et al., "Cerebrospinal fluid F2-isoprostane levels are increased in Alzheimer's disease," *Ann Neurol.* 1998 Sep;*44*(3):410-3.
			Ostrea et al., "Influence of breast-feeding on the restoration of the low serum concentration of vitamin E and beta-carotene in the newborn infant," *Am J Obstet Gynecol.* 1986 May;*154*(5):1014-7.
			Peunova et al., "Nitric oxide triggers a switch to growth arrest during differentiation of neuronal cells," *Nature.* 1995 May 4;*375*(6526):68-73.
			Piasecki et al., "Coincidence between spontaneous release of interferon and tumor necrosis factor by colostral leukocytes and the production of a colostrinine by human mammary gland after normal delivery," *Arch Immunol Ther Exp (Warsz).* 1997;*45*(1):109-17.

EXAMINER	Date Considered

*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT	Atty. Docket No.: 265.0023 0101	Serial No.: 09/641,801
	Applicant(s): Stanton et al.	Confirmation No.: 5388
	Filing Date: August 17, 2000	Group: 1653

			Popik et al., "Colostrinin, a polypeptide isolated from early milk, facilitates learning and memory in rats," *Pharmacol Biochem Behav.* 1999 Sep;*64*(1):183-9.
			Prasad et al., "Regional membrane phospholipid alterations in Alzheimer's disease," *Neurochem Res.* 1998 Jan;*23*(1):81-8.
			Roberts II et al., "Formation of isoprostane-like compounds (neuroprostanes) in vivo from docosahexaenoic acid," *J Biol Chem.* 1998 May 29;*273*(22):13605-12.
			Rothe et al., "Flow cytometric analysis of respiratory burst activity in phagocytes with hydroethidine and 2',7'-dichlorofluorescin," *J Leukoc Biol.* 1990 May; *47*(5):440-8.
			Royall et al., "Evaluation of 2',7'-dichlorofluorescin and dihydrorhodamine 123 as fluorescent probes for intracellular H2O2 in cultured endothelial cells," *Arch Biochem Biophys.* 1993 May;*302*(2):348-55.
			Subbarao et al., "Autopsy samples of Alzheimer's cortex show increased peroxidation *in vitro*," *J Neurochem.* 1990 Jul;*55*(1):342-5.
			Shacter et al., "Differential susceptibility of plasma proteins to oxidative modification: examination by western blot immunoassay," *Free Radic Biol Med.* 1994 Nov;*17*(5):429-37.
			Singh et al., "Dietary intake, plasma levels of antioxidant vitamins, and oxidative stress in relation to coronary artery disease in elderly subjects," *Am J Cardiol.* 1995 Dec 15;*76*(17):1233-8.
			Smith et al., "Advanced Maillard reaction end products are associated with Alzheimer disease pathology," *Proc Natl Acad Sci U S A.* 1994 Jun 7; *91*(12):5710-4.
			Smith et al., "Oxidative damage in Alzheimer's," *Nature.* 1996 Jul 11; *382*(6587):120-1.
			Smith et al., "Excess brain protein oxidation and enzyme dysfunction in normal aging and in Alzheimer disease," *Proc Natl Acad Sci U S A.* 1991 Dec 1; *88*(23):10540-3.

EXAMINER	Date Considered

*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT	Atty. Docket No.: 265.0023 0101	Serial No.: 09/641,801
	Applicant(s): Stanton et al.	Confirmation No.: 5388
	Filing Date: August 17, 2000	Group: 1653

			Svennerholm et al., "Membrane lipids, selectively diminished in Alzheimer brains, suggest synapse loss as a primary event in early-onset form (type I) and demyelination in late-onset form (type II), *J Neurochem.* 1994 Mar; *62*(3):1039-47.
			Takahashi et al., "Spontaneous transformation and immortalization of human endothelial cells," *In Vitro Cell Dev Biol.* 1990 Mar;*26*(3 Pt 1):265-74.
			Tsuchiya et al., "In vivo visualization of oxygen radical-dependent photoemission," *Methods Enzymol (Oxygen Radicals in Biological Systems).* 1994;*233C*:128-40.
			Villas et al., "Flow cytometry: an overview," *Cell Vis.* 1998 Jan-Feb;*5*(1):56-61
			Yan et al., "Glycated tau protein in Alzheimer disease: a mechanism for induction of oxidant stress," *Proc Natl Acad Sci U S A.* 1994 Aug 2;*91*(16):7787-91.
			Zimecki et al., "Effect of a proline-rich polypeptide (PRP) on the development of hemolytic anemia and survival of New Zealand black (NZB) mice," *Arch Immunol Ther Exp (Warsz).* 1991;*39*(5-6):461-7.

EXAMINER	Date Considered

*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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Exhibit A

Auto-Reply Facsimile Transmission

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PATENT
Docket No. 265.00230101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Stanton et al.	Group Art Unit:	1647
Serial No.:	09/641,801	Examiner:	C. Nichols
Confirmation No.:	5388		
Filed:	August 17, 2000		

For: USES OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

FACSIMILE TRANSMISSION TO THE PTO

Assistant Commissioner for Patents
Mail Stop AF
Attn: Examiner C. Nichols
P.O. Box 1450
Alexandria, VA 22313-1450

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Total Pages (including cover page): 15
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X Small Entity Status is entitled to be asserted in the above-identified application.

Please consider this a PETITION FOR EXTENSION OF TIME for a sufficient number of months to enter these papers and please charge any additional fees or credit overpayment to Deposit Account No. 13-4895.

Mueting, Raasch & Gebhardt, P.A.
Customer Number: 26813

26813

June 5, 2003
Date

By: Ann M. Mueting
Ann M. Mueting
Reg. No. 33,977
Direct Dial (612)305-1217

CERTIFICATE UNDER 37 C.F.R. §1.8: The undersigned hereby certifies that this Facsimile Cover Sheet and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office addressed to Assistant Commissioner for Patents, Mail Stop AF, P.O. Box 1450, Alexandria, VA 22313-1450, on this 5th day of June, 2003, at 5:15pm (Central Time).

June 5, 2003
Date

Signature: Sara E. Olson
Name: SARA E. OLSON

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PATENT
Docket No. 265.00230101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Stanton et al.	Group Art Unit:	1647
Serial No.:	09/641,801	Examiner:	C. Nichols
Confirmation No.:	5388		
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Assistant Commissioner for Patents
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Attn: Examiner C. Nichols
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X Small Entity Status is entitled to be asserted in the above-identified application.

Please consider this a PETITION FOR EXTENSION OF TIME for a sufficient number of months to enter these papers and please charge any additional fees or credit overpayment to Deposit Account No. 13-4895.

Mueting, Raasch & Gebhardt, P.A.
Customer Number: 26813

26813
PATENT TRADEMARK OFFICE

PATENT
Docket No. 265.00230101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Stanton et al.	Group Art Unit:	1647
Serial No.:	09/641,801	Examiner:	C. Nichols
Confirmation No.:	5388		
Filed:	August 17, 2000		

For: USES OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

AMENDMENT AND RESPONSE UNDER 37 CFR § 1.116

Assistant Commissioner for Patents
MAIL STOP AF
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action mailed March 5, 2003, please amend the above-identified application as follows:

In the Claims

Please amend claim 20. The amended claim is provided below in clean form. Per 37 C.F.R. §1.121, the amended claim is also shown in Appendix A with notations to indicate changes made (for convenience, all pending claims, are provided in Appendix A).

20. [Amended] A method for modulating leukocyte proliferation, the method comprising contacting leukocytes with a leukocyte regulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, under conditions effective to change the number of leukocytes; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

Remarks

The Office Action mailed March 5, 2003 has been received and reviewed. Claim 20 having been amended to correct a typographical error, the pending claims are claims 1-4, 6-9, 11, 13-35, and 37-39. Reconsideration and withdrawal of the rejections are respectfully

Examiner Interview

A telephonic Examiner's Interview was held on May 20, 2003 between the Applicants' representatives, Supervisory Patent Examiner Kunz and Patent Examiner Nichols, in which the outstanding restriction requirement was discussed. It was agreed upon that claims 20 and 29 qualify as linking claims. With the identification of allowable claims drawn to the elected species SEQ ID NO:1, non-elected species SEQ ID NO:2 -34 will be rejoined and examined upon indication of otherwise allowable subject matter. Examiners Kunz and Nichols are thanked for the courtesy of this telephonic interview.

Traverse of the Restriction Requirement

In response to the Restriction Requirement mailed June 17, 2002, Applicants elected, with traverse, Group 1 (claims 1-35), drawn to methods of contacting cells with SEQ ID NO:1 (Response to Restriction Requirement, filed July 17, 2002). Applicants continue to traverse this Restriction Requirement, noting that claims 20 and 29 are linking claims. Accordingly, the Examiner's restriction appears to be more appropriately an election of species with respect to specific sequences. See MPEP 809.02. Thus, Applicants traverse on the grounds that the generic (linking) claims 20 and 29 include sufficiently few species that a search and examination of all the species at one time would not impose a serious burden on the Examiner. Applicants also request rejoinder and that the requirement be withdrawn upon the finding of an allowable genus.

Objection to the Claims

The Examiner objected to claims 20-35 for the recitation of the non-elected inventions SEQ ID NO's 2-34. In view of the Applicants' request for the rejoinder of SEQ ID NO:2-34, discussed above, Applicants respectfully submit that this objection to the claims is moot. Withdrawal of this objection is respectfully requested.

The 35 U.S.C. §102 Rejection over Inglot et al.

The Examiner has maintained the rejection of claims 1-4 and 6-9 under 35 U.S.C. § 102 as being anticipated by Inglot et al. Specifically, the Examiner asserted that the NP peptide disclosed by Inglot anticipates the active analog, "wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1" of claims 1-4 and 6-9. In maintaining this rejection, the Examiner asserted that as the NP peptide of Inglot et al. is nine residues long and as the peptide of SEQ ID NO:1 is 7 residues long, "therefore NP is 77% structurally similar based on length, a structural characteristic, thus meeting the limitations of claims 1-4 and 6-9.

Applicants respectfully traverse this rejection. As defined on page 11, line 29 to page 12, line 2 of the specification, "[s]tructural similarity is generally determined by aligning the residues of two amino acid sequences to optimize the number of identical amino acids residues along the lengths of their sequences; gaps in either or both sequences are permitted in making the alignment in order to optimize the number of identical amino acids, although the amino acids in each sequence must nonetheless remain in their proper order." Thus, length alone does not establish "structural similarity." Rather, structural similarity is based on whether-or-not amino acid residues are identical, when compared one to another.

Applicants respectfully submit that the NP peptide of Inglot et al. does not have "at least about 70 percent structural similarity to SEQ ID NO:1." Thus, claims 1-4 and 6-9 are not anticipated by Inglot et al. and withdrawal of this rejection of the claims under 35 U.S.C. § 102 is respectfully requested.

The 35 U.S.C. §102 Rejection over Janusz et al.

The Examiner has maintained the rejection of claims 11 and 13-35 under 35 U.S.C. § 102 as being anticipated by Janusz et al. (WO 98/14473). This rejection is respectfully traversed.

Claims 11 are 13-19 are drawn to an immunological regulator, "wherein the immunological regulator comprises MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1." Claims 27 are 34 are drawn to a leukocyte regulator that is selected from the group of SEQ ID NO:1-34, "an active analog thereof, and combinations thereof; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34. Claims 28 and 35 are drawn to a leukocyte regulator selected from the group consisting of SEQ ID NO:1-8, SEQ ID NO:18-20, SEQ ID NO:22, and combinations thereof.

Applicants respectfully submit that Janusz et al. do not teach immunological regulators or leukocyte regulators that are the same as those claimed. As previously discussed, "structural similarity" is not determined by the mere comparison of length alone. Thus, the NP peptide of Janusz et al. does not have "at least about 70 percent structural similarity to SEQ ID NO:1," and claims 11, 13-19, 27, 28, 34, and 35 are not anticipated by Janusz et al.

Claims 20-28 are drawn to a "method for modulating leukocyte proliferation . . . comprising contacting leukocytes with a leukocyte regulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, *under conditions effective to change the number of leukocytes*" and claims 29-35 are drawn to a "method for modulating leukocyte proliferation in a patient . . . comprising administering to the patient a leukocyte regulator selected from the group of colostrinin, a constituent peptide thereof, an analog thereof, and combinations thereof, *under conditions effective to change the*

number of leukocytes." Claims 26 and 33 are further limited to "wherein the leukocyte regulator is a constituent peptide of colostrinin," and claims 27, 28, 34 and 35 are drawn leukocyte regulators selected from specific SEQ ID NO's, and active analogs thereof.

Applicants respectfully submit that Janusz et al. do not teach the claimed methods of modulating leukocyte proliferation, wherein modulating leukocyte proliferation is a change in the number of leukocytes. The Examiner asserted that "[o]nce administered, colostrinin would inherently and necessarily have caused an increase in leukocytes." And, citing Chapter 10 "Cytokines" of Elgert's "Immunology: Understanding the Immune System" textbook (pp. 199-217), the Examiner further asserted that "'growth, maturation, and differentiation' include proliferation or an increase in cell number" (see p. 8 of the Office Action mailed March 5, 2003). Applicants respectfully disagree.

Applicants are unable to locate within the cited pages of Elgert's Immunology textbook any statements that substantiate the Examiner's assertions. The Examiner is basing this rejection on the doctrine of inherency. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." M.P.E.P §2112 (emphasis in original). It is respectfully submitted that the Examiner has not met his burden of providing a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the cited documents.

Applicants respectfully submit that Janusz et al. does not teach a method of modulating leukocyte proliferation comprising contacting leukocytes with colostrinin under conditions effective to change the number of leukocytes and, thus, claims 20-35 are not anticipated by Janusz et al.

For the reasons discussed above, claims 11 and 13-35 are not anticipated by Janusz et al. Withdrawal of this rejection of the claims under 35 U.S.C. § 102 is respectfully requested.

Summary

It is respectfully submitted that the pending claims 1-4, 6-9, 11, 13-35, and 37-39 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
Stanton et al.

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

26813

PATENT TRADEMARK OFFICE

June 5, 2003
Date

By: Ann M. Mueting
Ann M. Mueting
Reg. No. 33,977
Direct Dial (612)305-1217

CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that this paper is being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Assistant Commissioner for Patents, Mail Stop AF, Alexandria, VA 22313-1450, on this 5th day of June, 2003, at 5:15 pm (Central Time).

By: Jane E. Olson
Name: JANE E. OLSON

APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS INCLUDING NOTATIONS TO INDICATE CHANGES MADE
Serial No.: 09/641,801
Docket No.: 265.00230101

Amendments to the following are indicated by underlining what has been added and bracketing what has been deleted.

In the Claims

For convenience, all pending claims are shown below.

1. A method of inducing a cytokine in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator comprises MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1.

2. The method of claim 1 wherein the cell is present in a cell culture, a tissue, an organ, or an organism.

3. The method of claim 1 wherein the cell is a mammalian cell.

4. The method of claim 3 wherein the cell is a human cell.

6. A method for modulating an immune response in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator comprises MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1.

7. The method of claim 6 wherein the cell is present in a cell culture, a tissue, an organ, or an organism.

8. The method of claim 6 wherein the cell is a mammalian cell.

9. The method of claim 8 wherein the cell is a human cell.

11. A method for modulating an immune response in a patient, the method comprising administering to the patient an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator comprises MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to SEQ ID NO:1.

13. The method of claim 11 wherein the immunological regulator is administered as part of a dietary supplement.

14. The method of claim 11 wherein the immunological regulator is administered topically.

15. The method of claim 11 wherein the patient is an animal.

16. The method of claim 15 wherein the patient is a human.

17. The method of claim 11 wherein the immune response is a specific immune response.

18. The method of claim 11 wherein the immune response is a nonspecific immune response.

19. The method of claim 11 wherein the immune response is the interferon response or antibody production.

20. [Amended] A method for modulating leukocyte proliferation, the method comprising contacting leukocytes with a leukocyte regulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, under conditions effective to change the number of leukocytes; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

21. The method of claim 20 wherein the leukocytes are present in a cell culture or an organism.

22. The method of claim 20 wherein the leukocytes are mammalian cells.

23. The method of claim 22 wherein the leukocytes are human cells.

24. The method of claim 22 wherein the leukocytes are increased in number.

25. The method of claim 24 wherein the leukocytes are differentiated.

26. The method of claim 22 wherein the leukocyte regulator is a constituent peptide of colostrinin.

27. The method of claim 26 wherein the leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2),

DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

28. The method of claim 27 wherein the leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8), YPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

29. A method for modulating leukocyte proliferation in a patient, the method comprising administering to the patient a leukocyte regulator selected from the group of colostrinin, a constituent peptide thereof, an analog thereof, and combinations thereof, under conditions effective to change the number of leukocytes; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

30. The method of claim 29 wherein the patient is a human.

31. The method of claim 29 wherein the leukocytes are increased in number.

32. The method of claim 31 wherein the leukocytes are differentiated.

33. The method of claim 29 wherein the leukocyte regulator is a constituent peptide of colostrinin.

34. The method of claim 33 wherein the leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID

NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

35. The method of claim 34 wherein the leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8),VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

37. A method of inducing a cytokine in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID

NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to a one or more constituent peptides of colostrinin which are selected from the group of SEQ ID NO:2-30 and 32-34.

38. A method for modulating an immune response in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30),

FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin which are selected from the group of SEQ ID NO:2-30 and 32-34.

39. A method for modulating an immune response in a patient, the method comprising administering to the patient an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin which are selected from the group of SEQ ID NO:2-30 and 32-34.

Receipt is hereby acknowledged for the following in the U.S. Patent and Trademark Office:
Applicant(s): Stanton et al.
Serial No.: 09/641,801
Filed: August 17, 2000
Title: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

Enclosed: A Petition for Extension of Time for 1 month; A Supplemental Information Disclosure Statement (2 pgs), copies of 0 applications; 1449 forms (3 pgs); and copies of 26 documents cited on the 1449 forms; Appointment of Associate Attorney (1 pg); Amendment and Response (18 pgs.); and transmittal document (in triplicate).

Please charge Deposit Account No. 13-4[illegible] in the following amounts:
$55.00 - Petition for Extension of Time
$180.00 - Supplemental Information Disclosure Statement Fee

Mailed: November 3, 2003
Docket: 265.00230101

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Stanton et al.	Group Art Unit:	1647
Serial No.:	09/641,801	Examiner:	Christopher Nichols
Confirmation No.:	5388		
Filed:	August 17, 2000		

For: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

AMENDMENT AND RESPONSE

Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action mailed July 3, 2003, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on the page entitled "Amendments to the Claims."

Remarks begin on the page entitled "Remarks."

Amendments to the Claims

This listing of claims replaces all prior versions, and listings, of claims in the above-identified application:

Listing of Claims

1. **(Currently Amended)** A method of inducing a cytokine in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator ~~comprises~~ consists of MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent ~~structural similarity~~ sequence identity to SEQ ID NO:1.

2. **(Original)** The method of claim 1 wherein the cell is present in a cell culture, a tissue, an organ, or an organism.

3. **(Original)** The method of claim 1 wherein the cell is a mammalian cell.

4. **(Original)** The method of claim 3 wherein the cell is a human cell.

5. **(Cancelled)**

6. **(Currently Amended)** A method for modulating an immune response in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator ~~comprises~~ consists of MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent

proline and having at least about 70 percent ~~structural similarity~~ sequence identity to SEQ ID NO:1.

7. **(Original)** The method of claim 6 wherein the cell is present in a cell culture, a tissue, an organ, or an organism.

8. **(Original)** The method of claim 6 wherein the cell is a mammalian cell.

9. **(Original)** The method of claim 8 wherein the cell is a human cell.

10. **(Cancelled)**

11. **(Currently Amended)** A method for modulating an immune response in a patient, the method comprising administering to the patient an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator ~~comprises~~ consists of MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent ~~structural similarity~~ sequence identity to SEQ ID NO:1.

12. **(Cancelled)**

13. **(Original)** The method of claim 11 wherein the immunological regulator is administered as part of a dietary supplement.

14. **(Original)** The method of claim 11 wherein the immunological regulator is administered topically.

15. **(Original)** The method of claim 11 wherein the patient is an animal.

16. **(Original)** The method of claim 15 wherein the patient is a human.

17. **(Original)** The method of claim 11 wherein the immune response is a specific immune response.

18. **(Original)** The method of claim 11 wherein the immune response is a nonspecific immune response.

19. **(Original)** The method of claim 11 wherein the immune response is the interferon response or antibody production.

20. **(Currently Amended)** A method for modulating leukocyte proliferation, the method comprising contacting leukocytes with a leukocyte regulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, under conditions effective to change the number of leukocytes; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent ~~structural similarity~~ sequence identity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

21. **(Previously Presented)** The method of claim 20 wherein the leukocytes are present in a cell culture or an organism.

22. **(Previously Presented)** The method of claim 20 wherein the leukocytes are mammalian cells.

23. **(Previously Presented)** The method of claim 22 wherein the leukocytes are human cells.

24. **(Previously Presented)** The method of claim 22 wherein the leukocytes are increased in number.

25. **(Previously Presented)** The method of claim 24 wherein the leukocytes are differentiated.

26. **(Previously Presented)** The method of claim 22 wherein the leukocyte regulator is a constituent peptide of colostrinin.

27. **(Currently Amended)** The method of claim 26 wherein the leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof; wherein the active analog comprises a peptide having an amino acid sequence with at least about

15 percent proline and having at least about 70 percent ~~structural similarity~~ sequence identity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

28. **(Previously Presented)** The method of claim 27 wherein the leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8), YPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

29. **(Currently Amended)** A method for modulating leukocyte proliferation in a patient, the method comprising administering to the patient a leukocyte regulator selected from the group of colostrinin, a constituent peptide thereof, an analog thereof, and combinations thereof, under conditions effective to change the number of leukocytes; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent ~~structural similarity~~ sequence identity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

30. **(Original)** The method of claim 29 wherein the patient is a human.

31. **(Previously Presented)** The method of claim 29 wherein the leukocytes are increased in number.

32. **(Previously Presented)** The method of claim 31 wherein the leukocytes are differentiated.

33. **(Previously Presented)** The method of claim 29 wherein the leukocyte regulator is a constituent peptide of colostrinin.

34. **(Currently Amended)** The method of claim 33 wherein the leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent ~~structural similarity~~ sequence identity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

35. **(Previously Presented)** The method of claim 34 wherein the leukocyte regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6),

VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8),VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

36. **(Cancelled)**

37. **(Withdrawn-Currently Amended)** A method of inducing a cytokine in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent ~~structural similarity~~ sequence identity to a one or more constituent peptides of colostrinin which are selected from the group of SEQ ID NO:2-30 and 32-34.

38. **(Withdrawn-Currently Amended)** A method for modulating an immune response in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent ~~structural similarity~~ sequence identity to one or more constituent peptides of colostrinin which are selected from the group of SEQ ID NO:2-30 and 32-34.

39. **(Withdrawn-Currently Amended)** A method for modulating an immune response in a patient, the method comprising administering to the patient an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6),

VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent ~~structural similarity~~ sequence identity to one or more constituent peptides of colostrinin which are selected from the group of SEQ ID NO:2-30 and 32-34.

Remarks

The Office Action mailed July 3, 2003, has been received and reviewed. The pending claims being claims 1-4, 6-9, 11, 13-35, and 37-39, claims 1, 6, 11, 20, 27, 29, 34, 37, 38, and 39 having been amended, and claims 37-39 having been withdrawn from examination, the claims under examination are claims 1-4, 6-9, 11, and 13-35. Reconsideration and withdrawal of the rejections are respectfully requested.

Examiner Interviews

A telephonic Examiner Interview was held on May 30, 2003, with Examiner Nichols, Supervisory Patent Examiner Kunz, and Applicants' Representatives, Ann Mueting and Nancy Johnson. Linking claim practice and the rejoinder of SEQ ID NO's 1-34 upon the identification of allowable claims were discussed. A second telephonic Examiner Interview was held on July 1, 2003, with Examiner Nichols, Supervisory Patent Examiner Kunz, and Applicants' Representative Nancy Johnson. The rejections of the claims as anticipated by Inglot et al. and Janusz et al. were discussed. Examiner Nichols and Supervisory Patent Examiner Kunz are thanked for the courtesy of these interviews.

Traverse of the Restriction Requirement

Applicants continue to traverse the Restriction Requirement mailed June 17, 2002, on the grounds that generic (linking) claims 20 and 29 include sufficiently few species that a search and examination of all the species at one time would not impose a serious burden on the Examiner. Applicants request that the requirement be withdrawn upon the finding of an allowable genus. Applicants also request the rejoinder of SEQ ID NO:2-34 and the rejoinder of claims 37-39.

The 35 U.S.C. §102 Rejection over Inglot et al.

The Examiner has maintained the rejection of claims 1-3 and 6-9 under 35 U.S.C. § 102 as being anticipated by Inglot et al. Applicants respectfully traverse this rejection. Applicants respectfully submit that Inglot et al. do not teach an immunological regulator, "wherein the immunological regulator consists of MQPPPLP (SEQ ID NO:1)." Thus, claims 1-3 and 6-9 are not anticipated by Inglot et al. and withdrawal of this rejection of the claims under 35 U.S.C. § 102 is respectfully requested.

The 35 U.S.C. §102 Rejection over Janusz et al.

The Examiner has maintained the rejection of claims 11 and 13-19 under 35 U.S.C. § 102 as being anticipated by Janusz et al. (WO 98/14473). The Examiner has also maintained the rejection of claims 20-35 under 35 U.S.C. § 102 as being anticipated by Janusz et al. (WO 98/14473). This rejection is respectfully traversed.

Applicants respectfully submit that Janusz et al. do not teach an immunological regulator, "wherein the immunoregulator consists of MQPPPLP (SEQ ID NO:1)." Thus, claims 11 and 13-19 are not anticipated by Janusz et al.

Claims 20-28 are drawn to a "method for modulating leukocyte proliferation . . . comprising contacting leukocytes with a leukocyte regulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, *under conditions effective to change the number of leukocytes*" and claims 29-35 are drawn to a "method for modulating leukocyte proliferation in a patient . . . comprising administering to the patient a leukocyte regulator selected from the group of colostrinin, a constituent peptide thereof, an analog thereof, and combinations thereof, *under conditions effective to change the number of leukocytes*." Claims 26 and 33 are further limited to "wherein the leukocyte regulator is a constituent peptide of colostrinin," and claims 27, 28, 34 and 35 are drawn leukocyte regulators selected from specific SEQ ID NO's, and active analogs thereof.

Applicants respectfully submit that Janusz et al. do not teach the claimed methods of modulating leukocyte proliferation, wherein modulating leukocyte proliferation is a change in the number of leukocytes. The Examiner asserted that "[o]nce administered, colostrinin would inherently and necessarily have caused an increase in leukocytes." And, citing Chapter 10 "Cytokines" of Elgert's "Immunology: Understanding the Immune System" textbook (pp. 199-217), the Examiner further asserted that "'growth, maturation, and differentiation' include proliferation or an increase in cell number" (see p. 8 of the Office Action mailed March 5, 2003). Applicants respectfully disagree.

Applicants are unable to locate within the cited pages of Elgert's Immunology textbook any statements that substantiate the Examiner's assertions. Further, the Examiner uses the doctrine of inherency to support these rejections. However, Applicants' Representatives submit that historically the inherency doctrine has been used to reject claims to a product that is alleged to be new when there is a process in the prior art that clearly yields the claimed product. The Examiner is requested to note that all the currently pending claims are directed to methods.

For inherency to apply, the missing descriptive information must necessarily be present in one of the cited documents such that one of skill in the art would recognize such a disclosure. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill'" (In re Robertson, 49 USPQ2d 1949 (Fed. Cir. 1999) quoting Continental Can Co. v. Monsanto Co., 20 USPQ2d 1746 (Fed. Cir. 1991)). See also MPEP 2112.

Applicants submit that there can be no recognition by one of skill in the art from the teachings of Janusz et al. that the modulation of leukocyte proliferation by contacting leukocytes with colostrinin under conditions effective to change the number of leukocytes is necessarily present. Inherency must be a necessary result, not merely a possible result. "'Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" (In re Robertson, 49

USPQ2d 1949 (Fed. Cir. 1999) quoting In re Oelrich, 212 USPQ 323 (Fed. Cir. 1981)). Furthermore, it is inherent only if there is at least a reasonable likelihood that one of skill in the art could have discovered or recognized it without specific guidance. That is, the subject matter relied upon must be disclosed in a manner to place it in possession of the public. (See, e.g., Akzo N.V. v. United States Int'l Trade Comm'n, 1 USPQ2d 1241 (Fed. Cir. 1986)). Clearly, this is not the situation with the documents cited by the Examiner.

Applicants respectfully submit that Janusz et al. do not teach a method of modulating leukocyte proliferation comprising contacting leukocytes with colostrinin under conditions effective to change the number of leukocytes and, thus, claims 20-35 are not anticipated by Janusz et al.

For the reasons discussed above, claims 11 and 13-35 are not anticipated by Janusz et al. Withdrawal of this rejection of the claims under 35 U.S.C. § 102 is respectfully requested.

Objection to the Claims

The Examiner objected to claims 1-4, 6-9, and 13-35 as reciting non-elected SEQ ID NO's. This objection is respectfully traversed. First, Applicants submit that claims 1-4, 6-9, 11, and 13-19 recite only SEQ ID NO:1, and thus, do not recite non-elected SEQ ID NO's. Second, in view of the Applicants' request for the rejoinder of SEQ ID NO:2-34, discussed above, Applicants respectfully submit that this objection to the claims is moot. Withdrawal of this objection is respectfully requested.

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claims 1-3, 6-9, 11, and 13-35 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner asserted that the metes and bounds of the recitation "structural similarity" are unclear. As previously

presented, Applicants submit that the metes and bounds of the recitation "structural similarity" are clear. However, to expedite prosecution, claims 1, 6, 11, 20, 27, 29, 34, and 37-39 have been amended to recite "sequence identity." Support for this recitation is found on page 11, lines 28-30 and page 12, lines 8-14 of the specification. Withdrawal of this rejection is respectfully requested.

Double Patenting Rejection

Claims 1-4, 6-9, 11, and 13-35 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,500,798. This rejection is respectfully traversed.

The claims of the instant invention are drawn to methods of inducing a cytokine in a cell, modulating an immune response in a cell, modulating an immune response in a patient, and modulating leukocyte proliferation. Specifically, claims 1-4 are drawn to "[a] method of inducing a cytokine in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine;" claims 6-9 are drawn to "[a] method for modulating an immune response in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine;" claims 11 and 13-19 are drawn to "[a] method for modulating an immune response in a patient, the method comprising administering to the patient an immunological regulator under conditions effective to induce a cytokine;" claims 20-28 are drawn to "[a] method for modulating leukocyte proliferation, the method comprising contacting leukocytes with a leukocyte regulator . . . under conditions effective to change the number of leukocytes;" and claims 29-35 are drawn to "[a] method for modulating leukocyte proliferation in a patient, the method comprising administering to the patient a leukocyte regulator . . . under conditions effective to change the number of leukocytes."

In contrast, claims 1-22 of U.S. Patent No. 6,500,798 are drawn to methods of modulating the oxidative stress level in a cell, modulating the oxidative stress level in a patient,

and treating oxidative damage to the skin of a patient. Specifically, claims 1-7 are drawn to "[a] method for modulating the oxidative stress level in a cell, the method comprising contacting the cell with an oxidative stress regulator under conditions effective to decrease the level of an oxidizing species present in the cell in response to an oxidative stress compared to the same conditions when the oxidative stress regulator is not present;" claim 8 is drawn to "[a] method for modulating the oxidative stress level in a cell, the method comprising contacting the cell with an oxidative stress regulator under conditions effective to prevent or reduce an increase in the level of an oxidizing species in the cell in response to an oxidative stress compared to the same conditions when the oxidative stress regulator is not present;" claims 9-16 are drawn to "[a] method for modulating the oxidative stress level in a patient, the method comprising administering to the patient an oxidative stress regulator under conditions effective to decrease the level of an oxidizing species present in the patient in response to an oxidative stress compared to the same conditions when the oxidative stress regulator is not present;" claim 17 is drawn to "[a] method for modulating the oxidative stress level in a patient, the method comprising administering to the patient an oxidative stress regulator under conditions effective to prevent or reduce an increase in the level of an oxidating species in the cell in response to an oxidative stress compared to the same conditions when the oxidative stress regulator is not present;" and, claims 18-22 are drawn to "[a] method of treating oxidative damage to the skin of a patient, the method comprising applying to skin a topical formulation comprising an oxidative stress regulator under conditions effective to prevent or reduce an increase in the level of damage to a biomolecule of the patient in response to an oxidative stress compared to the same conditions when the oxidative stress regulator is not present; wherein the biomolecule is selected from the group of a DNA, a protein, a lipid, or combinations thereof."

The Examiner asserted "it has been established by the courts that a product inherently possesses the characteristics of that product." Quoting *Ex parte Gray*, 10 USPQ 2d 1922 (1989) and *In re Best*, 195 USPQ 430 (1976), the Examiner further asserted "the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess

the characteristics of his claimed products." Finally, the Examiner asserted "[m]orover, when the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable, even though the prior art product was made by a different process." See page 4, ¶¶8-9, Office Action, mailed July 3, 2003. Applicants respectfully note that instant claims 1-4, 6-9, 11, and 13-35 are all drawn to methods, not products. Thus, these arguments provided by the Examiner have no relevance to the rejection of the instant method claims.

Further, Applicants acknowledge the Examiner's statement that the instant claims do "not practic[e] the preamble" of claims 1-22 of U.S. Patent No. 6,500,798" (page 4, ¶8, Office Action, mailed July 3, 2003). Applicants respectfully submit that method claims 1-4, 6-9, 11, and 13-35 differ from, and are not obvious in view of, claims 1-22 of U.S. Patent No. 6,500,798." The methods of modulating the oxidative stress level by contact with an oxidative stress regulator under conditions effective to decrease the level of an oxidizing species present in response to an oxidative stress, taught by claims 1-22 of U.S. Patent No. 6,500,798 do not teach or make obvious the claimed methods; methods of inducing a cytokine in a cell by contact with an immunological regulator under conditions effective to induce a cytokine, modulating an immune response by contact with an immunological regulator under conditions effective to induce a cytokine, and modulating leukocyte proliferation by contact with a leukocyte regulator under conditions effective to change the number of leukocytes. The methods of the instant claims differ from claims 1-22 of U.S. Patent No. 6,500,798 in effective goals and effective amounts administered, goals and effective amounts that are not taught by, or obvious over, claims 1-22 of U.S. Patent No. 6,500,798.

Applicants submit that claims 1-4, 6-9, 11, and 13-35 are not unpatentable over claims 1-22 of U.S. Patent No. 6,500,798. Withdrawal of this rejection under the judicially created doctrine of obviousness-type double patenting is respectfully requested.

Summary

It is respectfully submitted that the pending claims 1-4, 6-9, 11, 13-35, and 37-39 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
Stanton et al.

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

November 3, 2003
Date

By: Nancy A. Johnson
Nancy A. Johnson
Reg. No. 47,266
Direct Dial (612)305-4723

CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: EV 073735060 US Date of Deposit: November 3, 2003
The undersigned hereby certifies that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents,P.O. Box 1450, Alexandria, VA 22313-1450.

By: Sara E. Olson
Name: SARA E. OLSON

Exhibit A

Receipt is hereby acknowledged for the following in the U.S. Patent and Trademark Office:

Applicant(s): Stanton et al.
Serial No.: 09/641,801
Filed: August 17, 2000
Title: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

Enclosed: Amendment and Response (12 pgs.); Copies of 2 applications; and transmittal document (in triplicate).

Mailed: February 9, 2004
Docket: 265.00230101

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PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Stanton et al.	Group Art Unit:	1647
Serial No.:	09/641,801	Examiner:	Christopher Nichols
Confirmation No.:	5388		
Filed:	August 17, 2000		

For: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

AMENDMENT AND RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action mailed December 15, 2003, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on the page entitled "Amendments to the Claims."

Remarks begin on the page entitled "Remarks."

Amendments to the Claims

This listing of claims replaces all prior versions, and listings, of claims in the above-identified application:

Listing of Claims

1. **(Previously Presented)** A method of inducing a cytokine in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator consists of MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to SEQ ID NO:1.

2. **(Original)** The method of claim 1 wherein the cell is present in a cell culture, a tissue, an organ, or an organism.

3. **(Original)** The method of claim 1 wherein the cell is a mammalian cell.

4. **(Original)** The method of claim 3 wherein the cell is a human cell.

5. **(Cancelled)**

6. **(Previously Presented)** A method for modulating an immune response in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator consists of MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to SEQ ID NO:1.

7. **(Original)** The method of claim 6 wherein the cell is present in a cell culture, a tissue, an organ, or an organism.

8. **(Original)** The method of claim 6 wherein the cell is a mammalian cell.

9. **(Original)** The method of claim 8 wherein the cell is a human cell.

10. **(Cancelled)**

11. **(Previously Presented)** A method for modulating an immune response in a patient, the method comprising administering to the patient an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator consists of MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to SEQ ID NO:1.

12. **(Cancelled)**

13. **(Original)** The method of claim 11 wherein the immunological regulator is administered as part of a dietary supplement.

14. **(Original)** The method of claim 11 wherein the immunological regulator is administered topically.

15. **(Original)** The method of claim 11 wherein the patient is an animal.

16. **(Original)** The method of claim 15 wherein the patient is a human.

17. **(Original)** The method of claim 11 wherein the immune response is a specific immune response.

18. **(Original)** The method of claim 11 wherein the immune response is a nonspecific immune response.

19. **(Original)** The method of claim 11 wherein the immune response is the interferon response or antibody production.

20. **(Previously Presented)** A method for modulating leukocyte proliferation, the method comprising contacting leukocytes with a leukocyte regulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, under conditions effective to change the number of leukocytes; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

21. **(Previously Presented)** The method of claim 20 wherein the leukocytes are present in a cell culture or an organism.

22. **(Previously Presented)** The method of claim 20 wherein the leukocytes are mammalian cells.

23. **(Previously Presented)** The method of claim 22 wherein the leukocytes are human cells.

24. **(Previously Presented)** The method of claim 22 wherein the leukocytes are increased in number.

25. **(Previously Presented)** The method of claim 24 wherein the leukocytes are differentiated.

26. **(Previously Presented)** The method of claim 22 wherein the leukocyte regulator is a constituent peptide of colostrinin.

27. **(Currently Amended)** The method of claim 26 wherein the leukocyte regulator is selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

28. **(Currently Amended)** The method of claim 27 wherein the leukocyte regulator is selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD

(SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8), YPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

29. **(Currently Amended)** A method for modulating leukocyte proliferation in a patient, the method comprising administering to the patient a leukocyte regulator selected from the group consisting of colostrinin, a constituent peptide thereof, an analog thereof, and combinations thereof, under conditions effective to change the number of leukocytes; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

30. **(Original)** The method of claim 29 wherein the patient is a human.

31. **(Previously Presented)** The method of claim 29 wherein the leukocytes are increased in number.

32. **(Previously Presented)** The method of claim 31 wherein the leukocytes are differentiated.

33. **(Previously Presented)** The method of claim 29 wherein the leukocyte regulator is a constituent peptide of colostrinin.

34. **(Currently Amended)** The method of claim 33 wherein the leukocyte regulator is selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID

NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

35. **(Currently Amended)** The method of claim 34 wherein the leukocyte regulator is selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8),VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

36. **(Cancelled)**

37. **(Previously Presented)** A method of inducing a cytokine in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to a one or more constituent peptides of colostrinin which are selected from the group of SEQ ID NO:2-30 and 32-34.

38. **(Previously Presented)** A method for modulating an immune response in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV

(SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to one or more constituent peptides of colostrinin which are selected from the group of SEQ ID NO:2-30 and 32-34.

39. **(Previously Presented)** A method for modulating an immune response in a patient, the method comprising administering to the patient an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28),

RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to one or more constituent peptides of colostrinin which are selected from the group of SEQ ID NO:2-30 and 32-34.

Remarks

The Office Action mailed December 15, 2004 has been received and reviewed. Claims 27, 28, 29, 34, and 35 having been amended, the pending claims are claims 1-4, 6-9, 11, 13-35, and 37-39. The suggested amendments to claims 27, 28, 29, 34, and 35 have been made per the Examiner's request. Applicants thank the Examiner for his helpful suggestions.

The Examiner's attention is drawn to pending U.S. Application Serial No. 10/691,330, filed October 22, 2003 and U.S. Application Serial No. 10/691,157, filed October 22, 2003, as well as any documents, Office Actions that may include rejections of similar claims, and any provisional U.S. patent applications referenced in the pending U.S. applications or in their file wrappers. A copy of each of the pending U.S. Patent Applications is provided herewith.

Summary

It is respectfully submitted that in addition to claims 1-4, 6-9, 11, 13-26, 30-33, 37-39 which are allowed, the remaining pending claims 27-29, 34 and 35 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
Stanton et al.
By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

February 9, 2004
Date

By: Ann M. Mueting
Ann M. Mueting
Reg. No. 33,977
Direct Dial (612)305-1217

CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: EV 201890286 US Date of Deposit: February 9, 2004
The undersigned hereby certifies that the Transmittal Letter and the paper(s) and/or fee(s), as described hereinabove, are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Sandy Truehart
Name: Sandy Truehart

Exhibit A

Receipt is hereby acknowledged for the following in the U.S. Patent and Trademark Office:
Applicant(s): Stanton et al.
Serial No.: 09/641,801
Filed: August 17, 2000
Title: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

DKT 2

Enclosed: A Supplemental Information Disclosure Statement (2 pgs), copies of 0 applications; 1449 forms (4 pgs); and copies of 48 documents cited on the 1449 forms; Terminal Disclaimer (2 pgs.); Amendment and Response (13 pgs.); and transmittal document (in triplicate).

Please charge Deposit Account No. 13-[illegible] in the amount of $180.00 for the Supplemental Information Disclosure Statement Fee and $[illegible] for the Terminal Disclaimer Fee.

Mailed: July 28, 2004
Docket: 265.00230101

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PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Stanton et al.	Group Art Unit:	1647
Serial No.:	09/641,801	Examiner:	Christopher Nichols
Confirmation No.:	5388		
Filed:	August 17, 2000		

For: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

AMENDMENT AND RESPONSE

Commissioner for Patents
Mail Stop Amendment
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action mailed April 29, 2004, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on the page entitled "Amendments to the Claims."

Remarks begin on the page entitled "Remarks."

Amendments to the Claims

This listing of claims replaces all prior versions, and listings, of claims in the above-identified application:

Listing of Claims

1. **(Previously Presented)** A method of inducing a cytokine in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator consists of MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to SEQ ID NO:1.

2. **(Original)** The method of claim 1 wherein the cell is present in a cell culture, a tissue, an organ, or an organism.

3. **(Original)** The method of claim 1 wherein the cell is a mammalian cell.

4. **(Original)** The method of claim 3 wherein the cell is a human cell.

5. **(Canceled)**

6. **(Previously Presented)** A method for modulating an immune response in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator consists of MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog

comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to SEQ ID NO:1.

7. **(Original)** The method of claim 6 wherein the cell is present in a cell culture, a tissue, an organ, or an organism.

8. **(Original)** The method of claim 6 wherein the cell is a mammalian cell.

9. **(Original)** The method of claim 8 wherein the cell is a human cell.

10. **(Canceled)**

11. **(Previously Presented)** A method for modulating an immune response in a patient, the method comprising administering to the patient an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator consists of MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to SEQ ID NO:1.

12. **(Canceled)**

13. **(Original)** The method of claim 11 wherein the immunological regulator is administered as part of a dietary supplement.

14. **(Original)** The method of claim 11 wherein the immunological regulator is administered topically.

15. **(Original)** The method of claim 11 wherein the patient is an animal.

16. **(Original)** The method of claim 15 wherein the patient is a human.

17. **(Original)** The method of claim 11 wherein the immune response is a specific immune response.

18. **(Original)** The method of claim 11 wherein the immune response is a nonspecific immune response.

19. **(Original)** The method of claim 11 wherein the immune response is the interferon response or antibody production.

20. **(Currently Amended)** A method for modulating leukocyte proliferation, the method comprising contacting leukocytes with a leukocyte regulator selected from the group consisting of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, under conditions effective to change the number of leukocytes; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to one or more constituent peptides of colostrinin, which are selected from the group consisting of SEQ ID NO:1 through SEQ ID NO:34; and wherein the number of leukocytes is changed.

21. **(Previously Presented)** The method of claim 20 wherein the leukocytes are present in a cell culture or an organism.

22. **(Previously Presented)** The method of claim 20 wherein the leukocytes are mammalian cells.

23. **(Previously Presented)** The method of claim 22 wherein the leukocytes are human cells.

24. **(Previously Presented)** The method of claim 22 wherein the leukocytes are increased in number.

25. **(Previously Presented)** The method of claim 24 wherein the leukocytes are differentiated.

26. **(Previously Presented)** The method of claim 22 wherein the leukocyte regulator is a constituent peptide of colostrinin.

27. **(Currently Amended)** The method of claim 26 wherein the leukocyte regulator is selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof; wherein the active analog comprises a peptide having an amino acid sequence with at least about

15 percent proline and having at least about 70 percent sequence identity to one or more constituent peptides of colostrinin, which are selected from the group consisting of SEQ ID NO:1 through SEQ ID NO:34.

28. **(Previously Presented)** The method of claim 27 wherein the leukocyte regulator is selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8), YPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

29. **(Currently Amended)** A method for modulating leukocyte proliferation in a patient, the method comprising administering to the patient a leukocyte regulator selected from the group consisting of colostrinin, a constituent peptide thereof, an analog thereof, and combinations thereof, under conditions effective to change the number of leukocytes; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to one or more constituent peptides of colostrinin, which are selected from the group consisting of SEQ ID NO:1 through SEQ ID NO:34; and wherein the number of leukocytes is changed.

30. **(Original)** The method of claim 29 wherein the patient is a human.

31. **(Previously Presented)** The method of claim 29 wherein the leukocytes are increased in number.

32. **(Previously Presented)** The method of claim 31 wherein the leukocytes are differentiated.

33. **(Previously Presented)** The method of claim 29 wherein the leukocyte regulator is a constituent peptide of colostrinin.

34. **(Currently Amended)** The method of claim 33 wherein the leukocyte regulator is selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to one or more constituent peptides of colostrinin, which are selected from the group consisting of SEQ ID NO:1 through SEQ ID NO:34.

35. **(Previously Presented)** The method of claim 34 wherein the leukocyte regulator is selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPEP (SEQ ID NO:8),VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations thereof.

36. **(Canceled)**

37. **(Currently Amended)** A method of inducing a cytokine in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog

comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to a one or more constituent peptides of colostrinin which are selected from the group consisting of SEQ ID NO:2-30 and 32-34.

38. **(Currently Amended)** A method for modulating an immune response in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to one or more constituent peptides of colostrinin which are selected from the group consisting of SEQ ID NO:2-30 and 32-34.

39. **(Currently Amended)** A method for modulating an immune response in a patient, the method comprising administering to the patient an immunological regulator under conditions

effective to induce a cytokine, wherein the immunological regulator is a constituent peptide of colostrinin selected from the group consisting of LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to one or more constituent peptides of colostrinin which are selected from the group consisting of SEQ ID NO:2-30 and 32-34.

Remarks

The Office Action mailed April 29, 2004 has been received and reviewed. Claims 5, 10, 12, and 36 having been canceled, and claims 20, 27, 29, 34, and 37-39 having been amended, the pending claims are claims 1-4, 6-9, 11, 13-35, and 37-39. Reconsideration and withdrawal of the rejections are respectfully requested.

Double Patenting Rejection

Claims 1-4, 6-9, 11, 13-35, and 37-39 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,500,798. Claims 1-4, 6-9, 11, 13-35, and 27-39 were also rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent Application Serial No. 09/641,802. Submitted herewith is a Terminal Disclaimer which, Applicants submit, is in compliance with 37 CFR 1.321(c) and thereby obviates the Examiner's double patenting rejection of claims 1-4, 6-9, 11, 13-35, and 37-39

Claim Objection

In view of the amendment of claim 20 to recite "selected from the group consisting of," Applicants respectfully submit that the Examiner's objection to claim 20 is moot.

The 35 U.S.C. §102 Rejection

The Examiner rejected claims 20-35 under 35 U.S.C. §102(b) as being anticipated by Janusz et al. (*Molecular Immunology*; 24(10):1029-1031). The Examiner also rejected claims 20-35 under 35 U.S.C. §102(b) as being anticipated by Inglot et al. (*Archivum Immun Thera Exp*; 44(4):215-224). Applicants traverse the rejection of claims 20-35 as being anticipated by either Janusz et al. or Inglot et al. According to MPEP § 2131 a "claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."

Applicants respectfully submit that neither Janusz et al. nor Inglot et al. set forth each and every element of the methods of claims 20-35. Janusz et al. teaches that the administration of the colostrinin nonapeptide NP (SEQ ID NO:31) to mice enhances the primary immune response to sheep red blood cells (SRBC) in the mice (Janusz et al., page 1030). Inglot et al. teaches that colostrinin is a "modest inducer" of the cytokines IFN and TNF in human peripheral blood leukocytes and whole blood cultures and resulted in "psycho-stimulation" when orally administered to two human patients (see Inglot et al., abstract and page 215).

Claims 20-28 are drawn to "[a] method for modulating leukocyte proliferation, the method comprising contacting leukocytes with a leukocyte regulator . . . under conditions effective to change the number of leukocytes . . . wherein the number of leukocytes is changed," while claims 29-35 are drawn to "[a] method for modulating leukocyte proliferation in a patient, the method comprising administering to the patient a leukocyte regulator . . . under conditions effective to change the number of leukocytes . . . wherein the number of leukocytes is changed." In the claimed methods for modulating leukocyte proliferation, leukocytes are contacted with a leukocyte regulator (claims 20-28) or a leukocyte regulator is administered to a patient (claims 29-35) "under conditions effective to change the number of leukocytes . . . wherein the number of leukocytes is changed." Thus, in the claimed methods a leukocyte regulator is administered *under conditions effective to change the number of leukocytes,* and *wherein the number of leukocytes is changed.* Applicants respectfully submit that the Examiner's statements that claims 20-35 "are drawn to a method which comprises the step of contacting cells with an 'immunological regulator'" and that "[n]o other limitations are present in the claims" (pages 4 and 6 of the Office Action mailed April 29, 2004) are incorrect.

Applicants submit that neither Janusz et al. nor Inglot et al. teach administering a leukocyte regulator *under conditions effective to change the number of leukocytes* or *wherein the number of leukocytes is changed.* Thus, the disclosures of Janusz et al. or Inglot et al. do not set forth each and every element of claims 20-35. Withdrawal of this rejection under 35 U.S.C. §102(b) is respectfully requested.

Summary

It is respectfully submitted that the pending claims 1-4, 6-9, 11, 13-35, and 37-39 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
Stanton et al.

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

July 28, 2004
Date

By: Nancy A. Johnson
Nancy A. Johnson
Reg. No. 47,266
Direct Dial (612)305-4723

CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: EV201890414 US Date of Deposit: July 28, 2004
The undersigned hereby certifies that the Transmittal Letter and the paper(s) and/or fee(s), as described hereinabove, are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Sara E. Olson
Name: SARA E. OLSON

Exhibit A

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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NOTICE OF ALLOWANCE AND FEE(S) DUE

7590 11/02/2004

Mueting Raasch & Gebhardt PA
P O Box 581415
Minneapolis, MN 55458-1415

EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/02/2004

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/641,801	08/17/2000	G. John Stanton	265.0023 0101	5388

TITLE OF INVENTION: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF FOR INDUCING CYTOKINES

DKT 1

1/2/05 FORMALITIES
2/2/05 ISSUE/Pub Fee

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$685	$0	$685	02/02/2005

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 11/04) Approved for use through 04/30/2007.

Notice of Allowability	Application No. 09/641,801	Applicant(s) STANTON ET AL	
	Examiner Christopher J Nichols, Ph.D.	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *29 July 2004*.

2. ☒ The allowed claim(s) is/are *1-4, 6-9, 11, 13-35, 40-44*.

3. ☒ The drawings filed on *17 August 2000* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 7.29.04
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

11/01/2004 GTRAMMEL 00000006 09641801
01 FC:2202 3.00 DA 134635

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Supplemental Response filed 22 June 2004 has been received and entered in full.

2. The Response and Amendment filed 17 May 2004 has been received and entered in full.

3. The Terminal Disclaimer filed 22 July 2004 has been received and entered in full.

Withdrawn Objections And/Or Rejections

4. All previous Objections and Rejections are hereby *withdrawn*.

EXAMINER'S AMENDMENT

5. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

In the Claims:

Claim 1 (Currently Amended) A method ~~of~~ for inducing a cytokine in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator ~~consists of MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least~~

~~about 70 percent sequence identity to SEQ ID NO:1~~ is selected from the group consisting of a constituent peptide of colostrinin, an active analog thereof, and combinations thereof;

wherein the constituent peptide of colostrinin is selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID KO:3), LFFFLPVGVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPCKVEVFPFP (SEQ ID NO:8), and MHQPPQPLPPTVMFP (SEQ ID NO:34); and

wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to a constituent peptide of colostrinin selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID KO:3), LFFFLPVGVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPCKVEVFPFP (SEQ ID NO:8), and MHQPPQPLPPTVMFP (SEQ ID NO:34) and wherein said active analog induces a cytokine.

Claim 2 (Original) The method of claim 1 wherein the cell is present in a cell culture, a tissue, an organ, or an organism.

Claim 3 (Original) The method of claim 1 wherein the cell is a mammalian cell.

Claim 4 (Original) The method of claim 3 wherein the cell is a human cell.

Claim 5 (Cancelled)

Claim 6 (Currently Amended) A method for modulating an immune response in a cell, the method comprising contacting the cell with an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator ~~consists of MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to SEQ ID NO:1~~ is selected from the group consisting of a constituent peptide of colostrinin, an active analog thereof, and combinations thereof;

wherein the constituent peptide of colostrinin is selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID KO:3), LFFFLPVGVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPCKVEVFPFP (SEQ ID NO:8), and MHQPPQPLPPTVMFP (SEQ ID NO:34); and

wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to a constituent peptide of colostrinin selected from the group consisting of

MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID KO:3), LFFFLPVGVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPCKVEVFPFP (SEQ ID NO:8), and MHQPPQPLPPTVMFP (SEQ ID NO:34) and wherein said active analog modulates an immune response.

Claim 7 (Original) The method of claim 6 wherein the cell is present in a cell culture, a tissue, an organ, or an organism.

Claim 8 (Original) The method of claim 6 wherein the cell is a mammalian cell.

Claim 9 (Original) The method of claim 8 wherein the cell is a human cell.

Claim 10 (Cancelled)

Claim 11 (Currently Amended) A method for modulating an immune response in a patient, the method comprising administering to the patient an immunological regulator under conditions effective to induce a cytokine, wherein the immunological regulator ~~consists of MQPPPLP (SEQ ID NO:1), an active analog thereof, and combinations thereof, wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to SEQ ID NO:1~~ is selected from the group

consisting of a constituent peptide of colostrinin, an active analog thereof, and combinations thereof;

wherein the constituent peptide of colostrinin is selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID KO:3), LFFFLPVGVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPCKVEVFPFP (SEQ ID NO:8), and MHQPPQPLPPTVMFP (SEQ ID NO:34); and

wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to a constituent peptide of colostrinin selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID KO:3), LFFFLPVGVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPCKVEVFPFP (SEQ ID NO:8), and MHQPPQPLPPTVMFP (SEQ ID NO:34) and wherein said active analog modulates an immune response.

Claim 12 (Cancelled)

Claim 13 (Original) The method of claim 11 wherein the immunological regulator is administered as part of a dietary supplement.

Claim 14 (Original) The method of claim 11 wherein the immunological regulator is administered topically.

Claim 15 (Original) The method of claim 11 wherein the patient is an animal.

Claim 16 (Original) The method of claim 15 wherein the patient is a human.

Claim 17 (Original) The method of claim 11 wherein the immune response is a specific immune response.

Claim 18 (Original) The method of claim 11 wherein the immune response is a nonspecific immune response.

Claim 19 (Original) The method of claim 11 wherein the immune response is the interferon response or antibody production.

Claim 20 (Currently Amended) A method for modulating leukocyte proliferation, the method comprising contacting leukocytes with a leukocyte regulator selected from the group consisting of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, under conditions effective to change the number of leukocytes;

wherein the constituent peptide of colostrinin is selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID KO:3), LFFFLPVGVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPCKVEVFPFP (SEQ ID NO:8), VESYVPLFP (SEQ ID NO:31), and MHQPPQPLPPTVMFP (SEQ ID NO:34);

wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to ~~one or more constituent peptides of colostrinin, which are selected from the group consisting of SEQ ID NO: 1 through SEQ ID NO: 34;~~ a constituent peptide of colostrinin selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID KO:3), LFFFLPVGVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPCKVEVFPFP (SEQ ID NO:8), VESYVPLFP (SEQ ID NO:31), and MHQPPQPLPPTVMFP (SEQ ID NO:34);

and wherein the number of leukocytes is changed.

Claim 21 (Previously Presented) The method of claim 20 wherein the leukocytes are present in a cell culture or an organism.

Claim 22 (Previously Presented) The method of claim 20 wherein the leukocytes are mammalian cells.

Claim 23 (Previously Presented) The method of claim 22 wherein the leukocytes are human cells.

Claim 24 (Currently Amended) The method of claim ~~22~~ 20 wherein the leukocytes are increased in number.

Claim 25 (Previously Presented) The method of claim 24 wherein the leukocytes are differentiated.

Claim 26 (Currently Amended) The method of claim ~~22~~ 20 wherein the leukocyte regulator is a constituent peptide of colostrinin.

Claim 27 (Currently Amended) The method of claim ~~26~~ 20 wherein the leukocyte regulator is ~~selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID~~

~~NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30),~~ the colostrinin constituent peptide VESYVPLFP (SEQ ID NO:31), ~~FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34),~~ an active analog thereof, ~~and combinations~~ or a combination thereof~~, wherein the active analog comprises a peptide having an amino acid sequence with at least about 70 percent sequence identity to one or more constituent peptides of colostrinin, which are selected from the group consisting of SEQ ID NO: 1 through SEQ ID NO: 34~~.

Claim 28 (Currently Amended) The method of claim ~~27~~ 20 wherein the leukocyte regulator is ~~selected from the group consisting of~~ the colostrinin constituent peptide MQPPPLP (SEQ ID NO:1), ~~LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations,~~ an active analog thereof, or a combination thereof.

Claim 29 (Currently Amended) A method for modulating leukocyte proliferation in a patient, the method comprising administering to the patient a leukocyte regulator selected from the group

consisting of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, under conditions effective to change the number of leukocytes;

wherein the constituent peptide of colostrinin is selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID KO:3), LFFFLPVGVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPCKVEVFPFP (SEQ ID NO:8), VESYVPLFP (SEQ ID NO:31), and MHQPPQPLPPTVMFP (SEQ ID NO:34);

wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent sequence identity to ~~one or more constituent peptides of colostrinin, which are selected from the group consisting of SEQ ID NO: 1 through SEQ ID NO: 34;~~ a constituent peptide of colostrinin selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID KO:3), LFFFLPVGVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPCKVEVFPFP (SEQ ID NO:8), VESYVPLFP (SEQ ID NO:31), and MHQPPQPLPPTVMFP (SEQ ID NO:34);

and wherein the number of leukocytes is changed.

Claim 30 (Original) The method of claim 29 wherein the patient is a human.

Claim 31 (Previously Presented) The method of claim 29 wherein the leukocytes are increased in number.

Claim 32 (Previously Presented) The method of claim 31 wherein the leukocytes are differentiated.

Claim 33 (Previously Presented) The method of claim 29 wherein the leukocyte regulator is a constituent peptide of colostrinin.

Claim 34 (Currently Amended) The method of claim ~~33~~ 29 wherein the leukocyte regulator ~~is selected from the group consisting of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28),~~

~~RGPFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30),~~ is the colostrinin constituent peptide VESYVPLFP (SEQ ID NO:31), ~~FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34),~~ an active analog thereof, ~~and combinations~~ or a combination thereof~~; wherein the active analog comprises a peptide having an amino acid sequence with at least about 70 percent sequence identity to one or more constituent peptides of colostrinin, which are selected from the group consisting of SEQ ID NO: 1 through SEQ ID NO: 34~~.

Claim 35 (Currently Amended) The method of claim ~~34~~ 29 wherein the leukocyte regulator is the colostrinin constituent peptide ~~selected from the group consisting of~~ MQPPPLP (SEQ ID NO:1), ~~LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFLPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), and combinations,~~ an active analog thereof, ~~and combination~~ or a combination thereof.

Claims 36-39 (Cancelled)

Claim 40 (New) The method of claim 29 wherein the leukocyte regulator is administered as part of a dietary supplement.

Claim 41 (New) The method of claim 29 wherein the leukocyte regulator is administered topically.

Claim 42 (New) The method of claim 1 wherein the immunological regulator is the colostrinin constituent peptide MQPPPLP (SEQ ID NO: 1), an active analog thereof, or a combination thereof.

Claim 43 (New) The method of claim 6 wherein the immunological regulator is the colostrinin constituent peptide MQPPPLP (SEQ ID NO: 1), an active analog thereof, or a combination thereof.

Claim 44 (New) The method of claim 11 wherein the immunological regulator is the colostrinin constituent peptide MQPPPLP (SEQ ID NO: 1), an active analog thereof, or a combination thereof.

6. Authorization for this examiner's amendment was given in a telephone interview with Nancy Johnson on 20 October 2004.

7. Additional claims are required in order to make an examiner's amendment that places this application in condition for allowance. During a telephone conversation conducted on 28 October 2004, Nancy Johnson authorized the Director to charge Deposit Account No. 13-4895 the required fee of $40 for these additional claims and authorized the following examiner's amendment. Should the changes and/or additions be unacceptable to applicant, an amendment

may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Summary

8. Claims **1-4, 6-9, 11, 13-35,** and **40-44** are hereby allowed.

9. The Examiner acknowledges that acceptance of the above Examiner's Amendment does not mitigate in any way, shape, or form, Applicant's right to pursue additional subject matter in continuation, continuation-in-part, and/or divisional applications pursuant to 35 U.S.C. §120 and §121.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback** can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Elizabeth C. Kemmerer

CJN
October 20, 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER

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